IN THE UNITED STATES
PATENT AND TRADEMARK OFFICE

Applicant(s):   Kohn et al.

Application No: (not assigned)

Filing Date: (herewith)

Attorney Docket No: P-22577 G USA

Title: **Construction of Copolymer Libraries**

Art Group: (not assigned)

Examiner: (not assigned)

Assistant Commissioner for Patents
Box Patent Application
Washington, DC 20231

PATENT APPLICATION

Sir:

Enclosed are the following relating to the above mentioned application for patent:

Specification, Claims and Abstract
Drawings (8 sheets)
Combined Declaration and Power of Attorney (unexecuted)
Verified Statement Claiming Small Entity Status

CLAIMS AS FILED					
For	**# Filed**	**# Allowed**	**# Extra**	**Rate**	**Fee**
Total Claims	85	- 20 =	65	x $9.00	$585.00
Independent Claims	6	- 3 =	3	x $39.00	$117.00
Multiple Dependent Claims (check if applicable) ☐					$0.00
				BASIC FEE	$380.00
				TOTAL FILING FEE	$1,082.00

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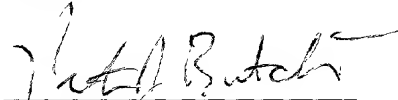__   A check in the amount of **$0.00** to cover the filing fee is enclosed.

xx   The Commissioner is hereby authorized to charge and credit Deposit Account No. **19-5425** as described below. A duplicate copy of this sheet is enclosed.

     xx   Charge the amount of $1,082.00   as filing fee.

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     __   Charge the issue fee set in 37 C.F.R. 1.18 at the mailing of the Notice of Allowance, pursuant to 37 C.F.R. 1.311(b).

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             Respectfully submitted,

Dated: April 13, 1999   _____
                       Peter J. Butch III
                       (Reg. No. 32,203)

Applicant or Patentee: Kohn et al.

Serial or Patent No.: _____

Filed or Issued: Herewith _____

For: THE CONSTRUCTION OF COMINATORIALLY DESIGNED COPOLYMER LIBRARIES

Attorney's
Docket No. OCIRS 3.0-056

VERIFIED STATEMENT (DECLARATION) CLAIMING SMALL ENTITY STATUS
(37 CFR 1.9(f) and 1.27(d)) - NONPROFIT ORGANIZATION

I hereby declare that I am an official empowered to act on behalf of the nonprofit organization identified below:

NAME OF ORGANIZATION ___ Rutgers, The State University, A Specially Chartered Educational Institution Within The State of New Jersey ___

ADDRESS OF ORGANIZATION Old Queens, Somerset Street, New Brunswick, New Jersey 08903

TYPE OF ORGANIZATION

[X] UNIVERSITY OR OTHER INSTITUTION OF HIGHER EDUCATION

[ ] TAX EXEMPT UNDER INTERNAL REVENUE SERVICE CODE (26 USC 501(a) and 501(c)(3))

[ ] NONPROFIT SCIENTIFIC OR EDUCATIONAL UNDER STATUTE OF STATE OF THE UNITED STATES OF AMERICA
    (NAME OF STATE_____)
    (CITATION OF STATUTE_____)

[ ] WOULD QUALIFY AS TAX EXEMPT UNDER INTERNAL REVENUE SERVICE CODE (26 USC 501(a) and 501(c)(3)) IF LOCATED IN THE UNITED STATES OF AMERICA

[ ] WOULD QUALIFY AS NONPROFIT SCIENTIFIC OR EDUCATIONAL UNDER STATUTE OF STATE OF THE UNITED STATES OF AMERICA IF LOCATED IN THE UNITED STATES OF AMERICA
    (NAME OF STATE_____)
    (CITATION OF STATUTE_____)

I hereby declare that the nonprofit organization identified above qualifies as a nonprofit organization as defined in 37 CFR 1.9(e) for purposes of paying reduced fees under Section 41(a) and (b) of Title 35, United States Code with regard to the invention entitled THE CONSTRUCTION OF COMINATORIALLY DESIGNED COPOLYMER LIBRARIES by inventor(s) Joachim B. Kohn, Stephen Brocchini, Kenneth James, and Varawut Tangpasuthadol described in

[X]   the specification filed herewith

[ ]   Application Serial No. _____, filed _____.

[ ] Patent No. _____, issued _____.

hereby declare that rights under contract or law have been conveyed to and remain with the nonprofit organization with regard to the above-identified invention.

If the rights held by the nonprofit organization are not exclusive, each individual, concern or organization having rights to the invention is listed below* and no rights to the invention are held by any person, other than the inventor, who could not qualify as a small business concern under 37 CFR 1.9(d) or by any concern which would not qualify as a small business concern under 37 CFR 1.9(d) or a nonprofit organization under 37 CFR 1.9(e). *NOTE: Separate verified statements are required from each named person, concern or organization having rights to the invention averring to their status as small entities. (37 CFR 1.27)

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        [ ] INDIVIDUAL   [ ] SMALL BUSINESS CONCERN   [ ] NONPROFIT ORGANIZATION

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acknowledge the duty to file, in this application or patent, notification of any change in status resulting in loss of entitlement to small entity status prior to paying, or at the time of paying, the earliest of the issue fee or any maintenance fee due after the date on which status as a small entity is no longer appropriate. (37 CFR 1.28(b))

hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this verified statement is directed.

NAME OF PERSON SIGNING____ William T. Adams _____

TITLE IN ORGANIZATION ____ Director, Office of Corporate Liaison and Technology Transfer ____

ADDRESS OF PERSON SIGNING, Administrative Services Building, Annex II, Bevier Road, Piscataway, NJ 08855

SIGNATURE _____   DATE 3/4/98

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THE CONSTRUCTION OF COPOLYMER LIBRARIES

CROSS-REFERENCE TO RELATED APPLICATION

The present invention claims priority benefit of U.S. Patent Application Serial No. 60/081,502, the disclosure of which is incorporated herein

5   by reference.

GOVERNMENT LICENSE RIGHTS

The U.S. government has a paid-up license in this invention and the right in limited circumstances to require the patent owner to license others on reasonable terms as required by the terms of Grant No. GM-49849 awarded by the

10   National Institutes of Health.

BACKGROUND OF THE INVENTION

The present invention relates to the construction of libraries of polymers based on the design principle of introducing systematic variations in the structure of a copolymer in at least two separate and independently variable

15   domains within the copolymer structure. The inventive methodology is broadly applicable to the development of copolymers where complex requirements necessitate a careful optimization of copolymer structure.

This invention is also related to the preparation of tyrosine-derived monomers as disclosed in U.S. Patent No. 5,587,507 and to the preparation and

20   use of polyarylates as disclosed in U.S. Patent Nos. 5,216,115 and 5,317,077, which are hereby incorporated by reference.

Combinatorial approaches that have led to dramatic changes in the way lead compounds for the discovery of new drugs are identified are disclosed by Lowe, JCS Reviews, 309-317 (1995). As usually practiced in the pharmaceutical

25   industry, combinatorial schemes are used to create a large number of structurally related compounds (almost always within a single reaction vessel) followed by the identification of potential lead compounds in a selective bioassay. Such combinational schemes are disclosed by Mischer, ChemTracts-Org. Chem., 8(1), 19-25 (1995). This approach is not readily applicable to the design of engineering

30   polymers or biomaterials. Starting with a mixture of monomers and creating a

large number of different polymers within the same reaction vessel would result in a blend of polymers that would be difficult to resolve into individual compounds. While such approaches are disclosed by EP 789,671 to be useful in the design of polymers with catalytic activities, these approaches are not useful for the design of

5 polymers where individual material properties need to be optimized.

Correlations between chemical structure and the properties of polymers were explored since the early 1930's when the macromolecular structure of polymers was first recognized. Sometimes, materials are studied in "sets" of structurally unrelated materials. For example, studying the tensile strength of

10 glass, iron, paper, wood, and polyethylene may lead to the identification of a material with suitable strength for any given application, however, because of the lack of any systematic variation in structure between the test materials, it is impossible to draw any generally useful conclusions from such a study.

A study design of somewhat greater sophistication is illustrated by

15 Ertel et al., J. Biomed. Mater. Res., 28, 919-930 (1994). A group of four polymers was investigated that had identical backbone structures but differed in the length of an alkyl ester pendent chain attached to the polymer backbone at each repeat unit. In this study, a relatively small number of polymers were compared and valid conclusions were drawn regarding the effect of increasing pendent chain

20 length on selected polymer properties such as glass transition temperature, rate of chemical degradation etc. It is estimated that hundreds of studies of this kind have been reported in the literature. The main limitation of this study design is that only one single structural variable can be explored.

A study design of greater complexity attempts to correlate the effect

25 of two or more structural variables on a set of selected materials properties. For example in the field of poly(acrylic acid) derivatives, a limited number of studies attempted to correlate the effect of simultaneous variations within the chemical structure of the acrylate pendent chains. Although such studies are known in the literature, the general paradigm of combinatorial synthesis has never been applied

30 to the combinatorial synthesis of copolymers with systematic and defined structural features. In terms of the requirements for library design, this approach is unknown in the prior art.

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Menger et al., J. Org. Chem., 60, 6666-6667 (1995), exposed a preformed polymer with reactive pendent chains to a reaction mixture that contained a series of different reactants. As a random coupling procedure was initiated, random sequences of pendent chains were attached to the preexisting polymer backbone. In essence, this is an approach whereby an untraceable mixture of pendent chain sequences were all prepared at once. The individual sequences could not be isolated and no structurally defined materials were obtained. Rather, the entire mixture was tested for a specific catalytic activity and it was impossible to detect which particular pendent chain sequence was responsible for any observed catalytic activity.

Considering the cost and time required to identify carefully designed and optimized polymeric materials as "specialty polymers" in many different industrial, medical, and scientific applications, there is a great need to develop new paradigms and approaches that can (1) increase the number of candidate polymers available for any specific application and (2) systematize the study of correlations between polymer structure on one hand and material properties and performance on the other hand.

SUMMARY OF THE INVENTION

This need is met by the present invention. An important aspect of this invention is that systems of monomers is used in such a way that a large number of polymers can be synthesized in a parallel fashion so that each polymer contained within the resulting library is obtained in pure form in its own reaction vessel. One of the important advantages of this approach is that libraries of polymers are obtained which facilitate the establishment of simple and useful correlations between systematic changes in the chemical composition of the polymers on one hand and a wide range of physicomechanical and biological properties on the other hand.

The practical utility of this approach depends on a chemical design that provides for the formation of copolymers of the type A-B, or A-B-C, and so forth. In the example of A-B type copolymers, two sets of reactants A_m and B_n, the copolymerization in all possible combinations of all monomers of set A with all

monomers of set B will give a library with a total of A x B products. It has now been established that if the A and B monomers possess deliberate structural design features, the resultant library will be endowed with informative permutations of these characteristics.

5   The usefulness of this approach in rapidly developing large arrays of polymers with systematically varying properties can be further illustrated by the extension of this principle to polymers that are derived of more than 2 monomeric species. For example, using an A-B-C terpolymer design, the copolymerization of a set of 10 A's with 10 B's and 10 C's will give rise to 1000 different

10   combinations. For sake of clarity, the following discussion is limited to strictly alternating A–B type copolymers with the understanding that the principles discussed can be readily extended to alternating polymers derived from more than two separate monomeric species.

        Therefore, in accordance with the present invention, it is now

15   possible to copolymerize a set of monomers derived from one structural template, with another set of monomers derived from a different structural template, so that the copolymerization of all members of the first set with all members of the second set in a preferably PARALLEL synthesis will lead to a library of copolymers in which the individual members of the library exhibit unusually systematic and

20   regular variations in key end-use properties. Therefore, according to one aspect of the present invention, a multi-dimensional copolymer array is provided, comprising a plurality of copolymers polymerized from at least two independently variable sets of monomers, wherein the polymerization is characterized by:

        (a)   selecting a first homologously varying series of monomers

25   with non-varying polymerizable functional groups;

        (b)   selecting at least one additional homologously varying series of different monomers having non-varying polymerizable functional groups that are reactive with the polymerizable functional groups of the first series of monomers to form copolymers; and

(c)   separately reacting a plurality of monomers from the first monomer series with a plurality of monomers from each of the additional monomer series to form the plurality of copolymers;

wherein the homologous variations of the monomer series are selected to determine the effect of independently varying at least two different structural features of the copolymer on at least one end-use property of the copolymer.

The copolymers include both condensation-type copolymers and copolymers prepared by free-radical polymerization. The homologous variations within each monomer series are preferably selected to minimize any effect upon the reactivity of the polymerizing functional groups of the monomers within each series.

For purposes of the present invention, homologous series are defined not only as relating to substituent groups on a series of monomers, but also including variations within the monomer backbone structure such as the introduction of unsaturation, the inclusion of additional methylene units, the replacement of a methylene carbon with a nitrogen or any other suitable atom, the replacement of a methylene unit with an oxygen or sulfur atom, or any other suitable atom, the replacement of a methylene unit with another unit including, but not limited to, a keto- unit, an amide unit, or an ester unit, and the like. For purposes of the present invention, hydrogen is treated as a member of homologous substituent series.

To obtain a library of polymers where selected end-use properties change in a predictable and systematic fashion, the monomer sets A and B must be designed to provide complementary structural variations. Preferred target end-use properties for investigation include glass transition temperature, surface tension, and biological interaction with living cells. The unique utility of such polymer libraries is twofold. The approach as described here can be used to (1) increase the number of candidate polymers available to be evaluated for any specific application and (2) systematize the study of correlations between polymer structure, end-use properties, and performance.
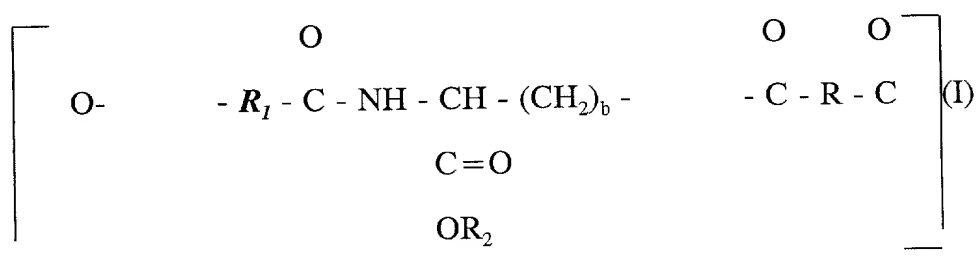
Therefore, according to another aspect of the present invention, a method is provided for determining the effect of independently varying at least two different structural features of a copolymer on an end-use property of the copolymer, which method includes the steps of:

5   (a)   measuring at least one end-use property of each of a plurality of copolymers prepared according to the present invention; and

(b)   comparing the variations in each end-use property measured for each of the copolymers as a function of the homologous variation within the monomer series from which the copolymers were polymerized to determine any

10   relationship between the homologous variations and the end-use property variations among the copolymers;

thereby identifying specific members of the plurality of copolymers having useful properties for specific end-uses.

Through the use of the inventive methodology it was unexpectedly

15   discovered that polyarylate copolymers, prepared by the condensation of a tyrosine-derived diphenol compound and a dicarboxylic acid, and having an ether linkage in either the polymer backbone or the polymer side chain were good cell growth substrates despite being very hydrophobic. Therefore, according to another aspect of the present invention, polyarylates are provided having repeating

20   units with the structure of Formula I:

$$\left[O- \quad -R_1 - \overset{\displaystyle O}{\overset{\displaystyle \|}{C}} - NH - CH - (CH_2)_b - \quad \underset{\underset{OR_2}{\overset{\displaystyle |}{C=O}}}{} \quad -\overset{\displaystyle O}{\overset{\displaystyle \|}{C}} - R - \overset{\displaystyle O}{\overset{\displaystyle \|}{C}} \right] \text{(I)}$$

25

wherein R is selected from saturated and unsaturated, substituted and unsubstituted, alkyl and alkylaryl groups containing up to 18 carbon atoms;

R_1 is selected from $-CH=CH-$, $(-CH_2-)_a$ and $-CHN(L_1L_2)-$, in which a has a value from zero to eight, inclusive, and L_1 and L_2 are independently
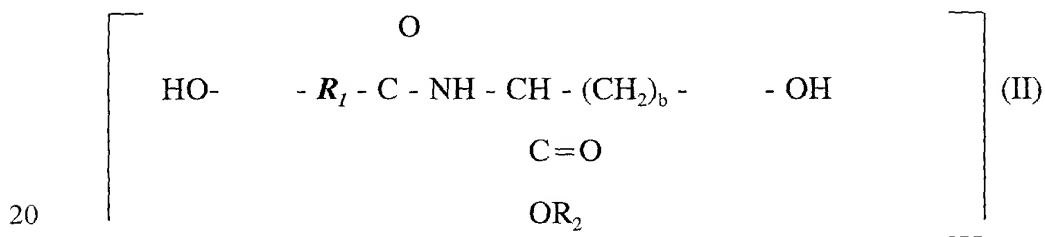
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selected from hydrogen and straight and branched alkyl and alkylaryl groups having up to 18 carbon atoms, provided that L_1 and L_2 are not both hydrogen;

b independently has a value from zero to eight, inclusive; and

R_2 is selected from hydrogen and straight and branched alkyl and

5   alkylaryl groups containing up to 18 carbon atoms;

wherein one or more of R, and R_2 and, when R_1 is $-CHNL_1L_2$, L_1 and L_2, contain at least one ether linkage.

The polyarylate copolymers of the present invention having ether linkage-containing side chains are the condensation product of a dicarboxylic acid

10   with a tyrosine-derived diphenol compound having at least one side chain containing at least one ether linkage. These diphenol compounds are novel and non-obvious in view of their unexpected ability to condense with a dicarboxylic acid to form a polyarylate copolymer that is unexpectedly both a good cell growth substrate and very hydrophobic. Therefore, according to another aspect of the

15   present invention, a tyrosine-derived diphenol compound is provided having the structure of Formula II:

$$\left[\text{HO-} \quad -R_1 - \overset{\displaystyle \overset{\text{O}}{\|}}{\text{C}} - \text{NH} - \underset{\underset{\displaystyle \underset{\text{OR}_2}{|}}{\overset{\displaystyle |}{\text{C}=\text{O}}}}{\text{CH}} - (\text{CH}_2)_b - \quad -\text{OH} \right] \quad \text{(II)}$$

20

wherein R_1, R_2, and b are the same as described above with respect to Formula I, with the proviso that R_2, and/or, when R_1 is $-CHNL_1L_2$, at least one of L_1 and L_2, contains at least one ether linkage.

25   A more complete appreciation of the invention and many other intended advantages can be readily obtained by reference to the following detailed description of the preferred embodiment and claims in conjunction with the accompanying drawings, which disclose the principles of the invention and the best modes which are presently contemplated for carrying them out.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 depicts the correlation between polymer glass transition temperature (T_g) and the chemical structure of polymer backbone (y axis) and pendent chain (x axis);

FIG. 2 depicts the correlation between the air-water contact angle (a measure of surface hydrophobicity and the chemical structure of polymer backbone (y axis) and pendent chain (x axis);

FIG. 3 depicts the general structure of polyarylates in accordance with the present invention;

FIGS. 4a and 4b depict the first and second homologous series of monomers employed in the method of the present invention to create the polyarylate copolymers of the present invention;

FIG. 5a depicts the correlation between T_g and the number of carbon atoms incorporated at the modification points of the polymer backbone and pendent chain, expressed as the total flexibility index (TFI);

FIG. 5b depicts the correlation between air-water contact angle and the number of carbon atoms incorporated at the modification points of the polymer backbone and pendent chain;

FIG. 6a depicts the correlation between T_g and the number of carbon atoms incorporated at the modification point of the polymer pendent chain;

FIG. 6b depicts the correlation between T_g and the number of carbon atoms incorporated at the modification point of the polymer backbone;

FIG. 7a depicts the correlation between fibroblast proliferation and surface hydrophobicity for poly(DT ester glutarates) and poly(DT ester glycolates); and

FIG. 7b depicts the correlation between fibroblast proliferation and surface hydrophobicity for poly(DT ester suberates) and poly(DT ester dioxaoctanedioates).

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

The general concept of the present invention and its application to biomaterials development is illustrated here for polyarylate copolymers prepared by the condensation of a diacid with a diphenol according to the method described by the above-referenced U.S. Patent No. 5,216,115, in which diphenol compounds are reacted with aliphatic or aromatic dicarboxylic acids in a carbodiimide mediated direct polyesterification using 4-(dimethyl-amino) pyridinium-p-toluene sulfonate (DPTS) as a catalyst. However, one of ordinary skill in the art will understand how this concept may be extended to other condensation or free radical polymerization reactions for other end-uses in addition to the preparation of biomaterials.

For example, in addition to monomer series in which the polymerizable functional groups are hydroxyl and carboxylic acid groups, other monomer series suitable for use with the present invention in condensation-type polymerization reactions include monomers having polymerizable amino, ester, anhydride, and isocyanate functional groups. The polymerizable functional group may also be activated to react with the polymerizable functional groups of the other monomer series.

When the polymerizable functional group of the first monomer series is a hydroxyl or amino group, monomer series suitable for use as additional monomer series include monomer series in which the polymerizable functional group is a carboxylic acid, isocyanate, ester or anhydride group. For condensation reactions in which two additional monomer series are employed, the second additional monomer series include alkylene oxide monomers. Examples of suitable alkylene oxide monomers include ethylene oxide, propylene oxide, isopropylene oxide, butylene oxide, isobutylene oxide and block and random copolymer segments thereof.

Condensation-type polymerization reactions include both interfacial and suspension processes. However, the present invention also includes copolymers prepared by free radical processes including ionic polymerization processes.

The synthesis reactions may be performed in solution or in bulk and with or without a catalyst. The reaction products may be further modified by chemical reactions or by cross-linking. Such synthesis features are well-known to those of ordinary skill in the art and require no further explanation.

5   A particularly preferred monomer series for use as the first monomer series are the tyrosine-derived diphenol monomers of U.S. Patent Nos. 5,587,507 and 5,670,602, the disclosures of both of which are also incorporated herein by reference. The preferred diphenol monomers are desaminotyrosyl-tyrosine esters, which are referred to as DT esters. For purposes of the present

10   invention, the ethyl ester is referred to as DTE, the benzyl ester as DTBn, and so forth. Both patents disclose methods by which these monomers may be prepared. As noted above, the diphenol monomers may be employed in the synthesis of the polyarylates disclosed by U.S. Patent No. 5,216,115.

The general structure of polyarylates is shown in Figure 3. These

15   materials are strictly alternating A-B type copolymers consisting of a diacid component (the "A" monomers) and a diphenol component (the "B" monomers). The diacids allow for variation in the polymer backbone while the diphenols contain a moiety for appending and varying a pendent chain. While the diphenol is a tyrosine-derived dimer, it functions as a single monomer unit in the

20   condensation reactions of the present invention, so that the condensation product of the diphenol with the diacid is considered a strictly alternating polyarylate copolymer when a third homologous monomer series is not employed.

Each set of monomers was derived from a single structural template that was varied according to the schemes shown in FIG. 4. Care was taken to

25   include only those compounds within the monomer sets of diacids and diphenols that had roughly identical reactivity at their reactive groups. In this way all polymers within the library, when prepared under identical reaction conditions, were expected to reach comparable molecular weights. Based on the above selection criteria, a total of 8 different aliphatic diacids and 14 different diphenols

30   were identified for inclusion in the sets of monomers.

Next, a grid of small reaction vessels was set up within a water shaker bath so that each reaction vessel contained one of the 8 x 14 = 112 different monomer combinations. Although the addition of monomers and reagents was performed in a manual fashion in these initial feasibility studies, the

5   process of dispensing the appropriate monomers and reagents within the reaction vessels could be readily automated.

Molecular weights (Mw) for the entire library of 112 polyarylates ranged from 50,000 to 150,000 g/mole. Polymer polydispersities ranged from 1.4 to 2.0. These values indicate that all polymers contained within the library were

10 of sufficiently high molecular weight and of sufficiently similar polydispersity to allow meaningful comparisons of their respective material properties. All polymers had the expected chemical structure, as confirmed by ^{1}H-NMR spectrometry.

At least one end-use property of each polymer is then measured and

15 the variations in each measured end-use property are compared as a function of the homologous variations within the series of monomers to determine any relationship or lack thereof between the homologous variations and the series of monomers and the measured variations in end-use properties for the resulting polymers. The end-use properties may be measured simultaneously, serially or in a spatially selected

20 manner. Measurement techniques include ELISA, SAM, chromatographic methods, DSC, TGA, DMA and TMA. Microscopic techniques may also be employed, as well as processing methods such as extrusion, solvent casting, compression molding, injection molding and microencapsulation.

End-use properties that may be measured are typically physical

25 properties such as mechanical properties, viscoelastic properties, morphological properties, electrical properties, optical properties (such as polarizability), solute and gas permeability, thermal properties (including glass transition temperature and degradation properties), surface tension properties, and the like. Examples of morphological properties include liquid crystalline properties, phase-separated

30 microdomain formation, the short- and long-range order of polymer chains, and the like. Examples of electrical properties include, dipole properties, pizeoelectric properties, dielectric properties, and the like.

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Other end-use properties that may be measured include, but are not limited to, antibacterial activity, blood compatibility, tissue compatibility, drug release characteristics, biological interactions with living organisms, specifically the ability to support cell attachment and proliferation required for the construction

5   of scaffolds for tissue engineering, hydrolytic degradation *in vivo*, protein adsorption characteristics, and the like. Still more end-use properties that may be measured include, but are not limited to, processability, radiation stability, sterilizability, adhesive properties, hydrophobic characteristics (as measured by air-water contact angle and other techniques), a stability to specific reaction

10   conditions, and the like. For purposes of the present invention, end-use properties are also defined as including the use of the inventive method to identify monomers for condensation-type polymerization reactions that are sufficiently miscible for the condensation-type reaction to occur under interfacial or suspension polymerization process conditions.

15   Other end-use properties relate to self-assembly, aggregation (micelle formation) and the formation of ordered networks (gels) in aqueous or organic solutions. These properties are controlled by the hydrophilic-hydrophobic balance of the monomers used in the design of the polymeric libraries and are measured by rheological studies in solutions, dynamic light scattering, or by

20   visualization of self-assembled aggregates by microscopic techniques such as atomic force microscopy.

             Important mechanical end-use properties include tensile strength, Young's modulus and yield strength. An important thermal property is glass transition temperature. Other important end-use properties are surface tension,

25   air-water contact angle as a measure of hydrophobicity, and biological interactions with living cells.

             FIG. 1 depicts the glass transition temperature (T_g) and FIG. 2 depicts the contact angle values for each of the 112 polymers. These histograms illustrate how the values for T_g and contact angle incrementally varied over a wide

30   range. T_g values ranged from 2-91 °C and increased in about 1 °C intervals from

polymer to polymer while air-water contact angles ranged from 64-101° and increased in about 0.5° intervals from polymer to polymer.

There are two useful ways to create more detailed correlations that include a larger number of polymers. First, it is possible to keep the polymer backbone composition constant while varying the polymer pendent chain of the diphenol repeating unit. For example, all polymers prepared from succinic acid but carrying different pendent chain alkyl esters would be such a subgroup. Second, it is possible to look at subgroups of polymers where the pendent chain is kept constant while the polymer backbone derived from the diacid repeating unit is varied. All polymers carrying a methyl ester pendent chain but containing different diacids would be such a subgroup. Using this approach, more detailed correlations examining selected subsets of polymers within the library were developed.

FIGS. 5a and 5b depict structure-property correlations within a subset of 72 polymers whose variable regions ("Y" and "R" in FIG. 4) were aliphatic, non-oxygen containing moieties. The total flexibility index (TFI) was defined as the number of carbon atoms incorporated at the modification points in the backbone and pendent chain. The exclusion of polymers containing oxygen atoms within their variable regions made it possible to isolate the effects related to the steric bulk of the pendent chain and the mobility/flexibility of the polymer backbone.

Plots of T_g and contact angle values versus TFI for these polymers are shown in FIG. 5a. These plots indicate that as TFI increases the T_g values decreased in an exponential fashion and that T_g values were modeled by the curve fitting equation shown in FIG. 5a. Air-water contact angles correlated with TFI in a linear fashion (FIG. 5b). Overall, varying the number of methylene groups in either the pendent chain or backbone were effective means for changing T_g and contact angle over a wide range and in a predictable fashion.

More specific correlations of T_g and contact angle dependence on the chemical structure of the backbone and pendent chain are shown in FIGS. 6A and 6B, which are two plots illustrating how T_g varies with increasing numbers of

methylene groups in the pendent chain and backbone respectively. Each point in these plots represents one specific polymer (excluding polymers with branched, aromatic, and oxygen-containing variable regions "R" and "Y"). The T_g values decreased exponentially as methylene groups were added to either the pendent

5   chain or backbone. The exponential curves are non-intersecting and similar in shape indicating that alterations in either the pendent chain or backbone produced a similar change in T_g.

Also noteworthy of this polyarylate library is that select polymers have glass transition temperatures close to or below body temperature. Hence,

10   devices made of these polymers can be designed to remain either in a glassy state or to assume a rubbery state when implanted.

An analogous set of plots are shown in FIGS. 7a and 7b for changes in contact angle. In contrast, there was a linear increase in the air-water contact angle as methylene groups were added to either the pendent chain or backbone.

15   Also, unlike the T_g relationships, alterations in the pendent chain or backbone produced different changes in the contact angle. The steeper curve slopes observed in the graph of contact angle vs. pendent chain suggests that surface hydrophobicity was more efficiently influenced by varying the number of methylene groups in the pendent chain. The slopes were also greater for

20   modifications on the lower methylene homologues compared to the higher homologues.

Thus, the addition of methylene groups to the pendent chain had a greater relative effect in the succinate polymers than in the sebacate polymers. It is noteworthy that such detailed and predictive correlations between polymer

25   structure and physical properties cannot usually be obtained in the absence of the combinatorial approach described here.

Backbone branching was studied with the 3-methyl adipate series of polymers. Keeping the diphenol pendent chain constant and varying the diacid backbone was found to modestly effect T_g ranging from a 2°C increase to a 5°C

30   decrease with an overall average decrease of 1°C. Pendent chain branching studied with the iso- and sec-butyl esters, while keeping the diacid backbone

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constant, caused an average 6°C (range 3-10°C) increase in T_g over the linear pendent chain polymers. Branching at either the pendent chain or the backbone had little discernible influence on the surface hydrophobicity as measured by the air-water contact angle.

5   FIGS. 1 and 2 depict that the substitution of oxygen atoms in place of methylene groups in the diphenol pendent chain and the diacid backbone had a significant effect on the glass transition temperature. Oxygen substitution in the diacid backbone increased T_g. Comparing the glutarate series of polymers to the diglycolate series of polymers, the replacement of one single methylene group in

10   the diacid backbone with an oxygen atom resulted, on average, in an increase of 8°C (range 2-13°C) in the respective T_g values.

On the other hand, oxygen substitution in the diphenol pendent chain decreased T_g in a comparison of the DTG series of polymers to the comparable DTO series of polymers. The oxygen substituted DTG series had an

15   average T_g that was 13°C (range 11-15°C) less than the comparable fully hydrocarbon DTO series of polymers.

Oxygen substitution in either the backbone of the diacid or the pendent chain of the diphenol decreased the surface hydrophobicity of the polymers compared to the corresponding polymers having only methylene groups

20   in their variable regions. All polymers derived from dioxaoctanedioic acid exhibited, on average, an air-water contact angle 5° (range 0-10°) less than the corresponding polymers derived from suberic acid. Similarly, all the library polymers with the oxygen-containing DTG pendent chain had air-water contact angles that were on the average 10°C (range 2-17°C) less than the contact angles

25   of the corresponding DTO polymers. Still, some polymers such as poly(DTD diglycolate) (air water contact angle = 97°) had extremely hydrophobic surfaces in spite of the replacement of a methylene group by an oxygen atom in the polymer backbone.

The polyarylate library encompasses a broad range of mechanical

30   properties. In qualitative terms, the stiffest of the polyarylates has mechanical properties similar to poly(D,L-lactic acid), while the most flexible polymers within

the library have mechanical properties resembling those of soft polysiloxanes. The mechanical properties of a subset of eleven polymers chosen to represent a range of glass transition temperatures from 28°C to 78°C in approximately 5° intervals are listed in Table 1 in order of decreasing T_g. In this subset of materials,

5   Young's modulus varied from 0.28 - 1.68 GPa and yield strength ranged from 5.8 - 44.8 MPa. There are no observable incremental correlations between polymer structure and stiffness or yield strength. However, those polymers whose glass transition temperature was below 35°C showed a dramatic drop in stiffness and tensile strength that was related to their impending transition from the glassy into

10   the rubbery state.

TABLE I

ROOM TEMPERATURE (22°C) MECHANICAL PROPERTIES OF SELECTED POLYARYLATES

Polymer	T_g (°C)	Young's Modulus (GPa)	Yield Stress (Mpa)	Strain at Break (%)
poly(DTE succinate)	78	1.68 ± 0.17	40.7 ± 3.2	304 ± 102
poly(DTB succinate)	67	1.56 ± 0.18	44.8 ± 3.8	566 ± 36
poly(DTE adipate)	61	1.56 ± 0.10	42.0 ± 4.4	638 ± 152
poly(DTH succinate)	53	1.61 ± 0.10	44.8 ± 2.3	456 ± 103
poly(DTE suberate)	50	1.39 ± 0.10	39.9 ± 3.7	534 ± 91
poly(DTO succinate)	48	1.41 ± 0.18	41.9 ± 4.5	622 ± 68
poly(DTB adipate)	46	1.49 ± 0.22	40.5 ± 3.5	710 ± 96
poly(DTE sebacate)	44	1.44 ± 0.06	34.4 ± 3.1	657 ± 56
poly(DTB suberate)	37	1.24 ± 0.04	31.0 ± 0.8	138 ± 150
poly(DTB sebacate)	30	0.28 ± 0.03	5.8 ± 0.7	744 ± 50
poly(DTO adipate)	28	0.39 ± 0.09	7.6 ± 1.8	676 ± 86

One of the important aspects of this library of polymers is that some material properties remained reasonably constant throughout the entire library. For example, all 112 polymers had decomposition temperatures (measured by TGA, open pan, nitrogen atmosphere) above 300°C, all polymers were amorphous and readily soluble in common organic solvents (methylene chloride, chloroform, tetrahydrofuran, dimethylformamide). Thus, all polymers contained in the library could be readily processed by solvent casting, compression molding, and extrusion.

An unexpectedly systematic correlation between polymer structure and cellular response is a unique aspect of the library of polyarylates and was observed in vitro in a study of the proliferation of fibroblasts on growth surfaces prepared from a subgroup of 42 test polymers having a straight-chain diphenol pendent chain (methyl, ethyl, butyl, hexyl, octyl and dodecyl) in combination with seven straight-chain diacid backbone configurations.

Although the polymers are degradable under physiological conditions, release of leachable contaminants or degradation products is not observed and no mass loss occurs over a period of several months. Fibroblast proliferation ranged from approximating that typically seen on tissue culture polystyrene (TSPS) dishes (poly(DTM glutarate) and poly(DTM succinate)) to complete absence of any proliferation (poly(DTD adipate) and poly(DTD succinate)). In general, the proliferation of fibroblasts on materials derived from non-oxygen containing diacids exhibits a strong, linear correlation with the contact angle (FIGS. 7a and 7b). As indicated by the highly negative slopes of the curves, cell proliferation decreases as the air-water contact angle increases from 65-100°. This is in agreement with the general observation that more hydrophobic polymer surfaces are poorer cell growth substrates for fibroblasts.

Fibroblast proliferation is more sensitive to the chemical structure of the polymer than the absolute contact angle measurement. The series of polymers having a methyl ester pendent chain (DTM) are all excellent, almost equivalent growth substrates (average 91% of TCPS proliferation; range 79-115%) even though the contact angles range from 66° to 77°. Likewise, within the library there are several polymers that have comparable contact angles that support

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widely varying levels of cell proliferation. For example, poly(DTB sebacate) and poly(DTH adipate) have an air-water contact angle of 84°, yet cell proliferation (relative to TCPS) is 58% and 16% respectively. In other words, within each subgroup of polymers from the same diacid but having different pendent chains,

5   cell proliferation decreases linearly as methylene groups are successively added to the pendent chain. However, this decrease is not directly correlated with the absolute contact angle measurement of the surface and the slopes of the respective regression curves are different for each of the polymer subgroups. That is, the chemical structure of the diacid in the polymer backbone modulates the cellular

10   response to the pendent chains.

On those polymers where oxygen was substituted in the backbones (diglycolate and dioxaoctanedioates series), fibroblast proliferation was far less sensitive to pendent chain length and surface hydrophobicity. This correlation is illustrated in FIGS. 7a and 7b by the dramatically less negative slope of the linear

15   curve fit. All polymers having oxygen-containing diacids in their backbone are unexpectedly uniformly good fibroblast growth substrates irrespective of surface hydrophobicity.

A particularly striking example of the effect of oxygen substitution on the cellular response is the direct comparison of poly(DTD glutarate) and

20   poly(DTD diglycolate) (FIG. 7a). These two polymers have identical structures, except that one single methylene group in the backbone of poly(DTD glutarate) has been replaced by an oxygen atom in poly(DTD diglycolate). This small structural change has very little effect on the overall polymer properties and the two polymers have virtually identical air-water contact angles of 96° and 97°,

25   respectively. Yet fibroblasts do not proliferate on poly(DTD glutarate) to any significant extent, while substantial cell proliferation is observed on identical surfaces prepared from poly(DTD diglycolate). This is a valuable finding since it demonstrates that careful polymer design makes it possible to "decouple" the correlation between surface hydrophobicity and cell proliferation.

30   Ertel et al., J. Biomed. Mat. Res., 24, 1637-1659 (1990), and Steele et al., J. Biomater. Sci. Polymer Edn., 6(6), 511-532 (1994), have reported that incorporation of oxygen species into the surface by plasma glow discharge can

improve cell growth. This method incorporates oxygen species in a random fashion and is associated with a corresponding reduction in the air-water contact angle. In the polyarylate library of this invention, the selective replacement of a single methylene group by a single oxygen atom occurs at a specific position in the

5   polymer backbone and has little effect on the air-water contact angle while significantly improving the cell growth characteristics of the substrate. This finding is unprecedented in the current literature.

Therefore the present invention includes polyarylate copolymers having the structure of Formula I in which R, R_1, R_2 and b are the same as

10   described above with respect to Formula I and at least one of R, R_1 and R_2 contain an ether linkage. R_1 is preferably $-CH_2-CH_2-$ and b is preferably one. When R contains an ether linkage, R_2 is preferably hydrogen or an ethyl, butyl, hexyl, octyl or benzyl group.

R, when it contains an ether linkage, is preferably $-CH_2-O-CH_2-$ or

15    $-CH_2-O-CH_2-CH_2-O-CH_2-$. When R_1 or R_2 contain an ether linkage, R preferably, when aliphatic, contains from 4 to 12 carbon atoms. When aromatic, R preferably contains from 8 to 14 carbon atoms. R is even more preferably selected so that the dicarboxylic acids from which the polyarylates are polymerized are either important naturally-occurring metabolites or highly biocompatible compounds.

20   Preferred aliphatic dicarboxylic acids therefore include the intermediate dicarboxylic acids of the cellular respiration pathway known as the Krebs Cycle. These dicarboxylic acids include alpha-ketoglutaric acid, succinic acid, fumaric acid, maleic acid and oxalacetic acid. Other preferred biocompatible materials include sebacic acid, adipic acid, oxalic acid, malonic acid, glutaric acid, pimelic

25   acid, suberic acid and azelaic acid. Among the preferred aromatic dicarboxylic acids are terephthalic acid, isophthalic acid and bis(p-carboxyphenoxy) alkanes such bis(p-carboxyphenoxy) propane. R is most preferably selected from $-CH_2-C(=O)-$, $-CH_2-CH_2-C(=O)-$, $-CH=CH-$ and $(-CH_2-)_z$, wherein z is an integer between two and eight, inclusive.

30   R_1 can contain an ether linkage when it is either $-CHNHL_1$ or $-CHNL_1L_2$, wherein at least one ether linkage is located in the alkyl group of L_1 or L_2. When either R_1 or R_2, contains an ether linkage the moiety is preferably

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-CH_2-CH_2-O-CH_2-CH_2-O-CH_2-CH_2OH. Polyarylate copolymers in accordance with the present invention have weight average molecular weights between about 20,000 and 400,000 daltons, and preferably about 100,000 daltons, measured by GPC relative to polystyrene standards without further correction.
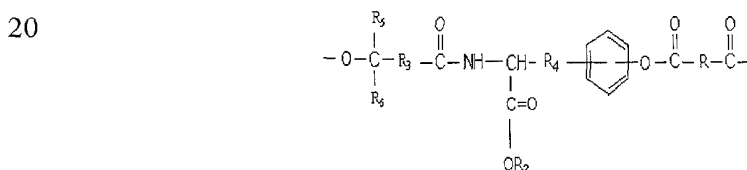
5   Tyrosine-derived diphenol monomers in which either R_1 or R_2 contain at least one ether linkage are also included within the scope of the present invention. Such monomers have the structure of Formula II, in which R_1, R_2 and b are the same as described above with respect to Formula II. R_1 is preferably -CH_2-CH_2-, in which case R_2 will contain an ether linkage, preferably the

10   aforementioned -CH_2-CH_2-O-CH_2-CH_2-O-CH_2-CH_2OH. If R_1 is either -$CHNHL_1$ or -$CHNL_1L_2$, wherein either L_1 or L_2 contains at least one ether linkage, then R_2 is preferably hydrogen or an ethyl, butyl, hexyl, octyl or benzyl group. The preferred ether linkage-containing moiety for L_1 or L_2 is also the aforementioned CH_3-CH_2-O-CH_2-CH_2-O-CH_2-CH_2OH-.

15   The two general features of the above-disclosed polyarylate copolymer library which dictated the choice of monomers were that specific properties including T_g, contact angle, mechanical properties and cellular response should vary incrementally over a wide range, and properties such as amorphous morphology, hydrolytic lability, processibility, and biocompatibility would remain

20   broadly similar. The advantage for this juxtaposition of property variability is that structurally similar polymers can be used in applications that are related in some general ways, but disparate in others. There are significant economic incentives in this approach for developing polymers because once a material from such a library establishes itself by successfully undergoing rigorous evaluation (e.g., FDA) for

25   an application, other library materials might then be more quickly developed for other applications. The above-described polyarylate copolymers were designed for use in medical applications requiring degradable materials. For example, a medical application might require a soft, pliable (low T_g) material which is hydrophobic (low contact angle), while another application might require a

30   relatively hard, stiff (higher T_g) material which is hydrophilic, while both applications may require properties that are commonly shared among all library

materials such as processibility by molding, biocompatibility, degradability, and amorphous morphology.

For the above-described polyarylate copolymers, the monomers were chosen to provide incremental differences in polymer free volume, bulkiness,
5   flexibility, and hydrophobicity. Corresponding structural variations in the two sets of monomers did not affect polymers properties equally. Thus, the monomer modifications were complementary because variation of the pendent chain did not have the same influence on polymer properties as the same modification to the polymer backbone. The three broad types of modification on the pendent chain
10   and backbone structure were (1) simple homologative type variations to vary the number of methylene groups, (2) substitution of oxygen for methylene groups, and (3) branching. The pendent chain modifications were all carried out with the tyrosine-derived diphenols which were prepared by a common synthetic process while backbone modifications were achieved by the judicious use of commercial
15   diacids and hydroxyphenyl alkyl acids.

Similar modifications are expected to provide useful results with the poly(amide esters) of WO 98/36013, the disclosure of which is incorporated herein by reference. The present invention therefore also includes poly(amide esters) having the structure:
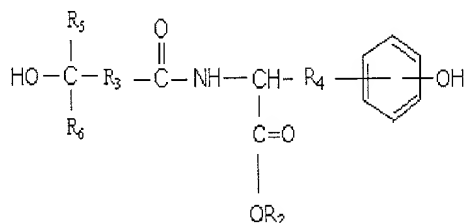
20

wherein R_3 is selected from -CH=CH-, $(-CH_2-)_a$, and $-CHN(L_1L_2)$, in which a has a value from zero to two, inclusive, and L_1 and L_2 are independent-
25   ly selected from hydrogen and straight and branched alkyl and alkylaryl groups containing up to 18 carbon atoms, provided that L_1 and L_2 are not both hydrogen. R_5 and R_6 are each independently selected from hydrogen and straight or branched alkyl groups having up to 18 carbon atoms and R_4 is $(-CH_2-)_b$, wherein b independently has a value between zero and eight, inclusive. R_2 is selected from straight
30   and branched alkyl and alkylaryl groups containing up to 18 carbon atoms, and R is selected from saturated and unsaturated, substituted and unsubstituted alkyl, aryl

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and alkylaryl groups containing up to 18 carbon atoms. At least one of R, R_2, R_5, R_6 and, when R_3 is -CHNL$_1$L$_2$, L$_1$ or L$_2$, contains at least one ether linkage.

R_3 is preferably (-CH$_2$-)$_a$, with a being zero, and R_5 and R_6 are preferably independently selected from hydrogen and methyl. Most preferably, at

5 least one of R_5 and R_6 is hydrogen, while the other, when not hydrogen is methyl. The value for b is preferably one. Thus, it is preferred that at least one of R and R_2 contain at least one ether linkage. Preferred ether and non-ether species for R and R_2 are the same as described above for the polyarylates of the present invention.

10   The present invention therefore also includes aliphatic-aromatic dihydroxy monomer compounds having the structure:

$$HO-\overset{\overset{\displaystyle R_5}{|}}{\underset{\underset{\displaystyle R_6}{|}}{C}}-R_3-\overset{\overset{\displaystyle O}{\|}}{C}-NH-\overset{\underset{\underset{\underset{\underset{\displaystyle OR_2}{|}}{C=O}}{|}}{}}{CH}-R_4-\langle\!\!\bigcirc\!\!\rangle-OH$$

15

        wherein R_3 is selected from -CH=CH-, (-CH$_2$-)$_a$, and -CHN(L$_1$L$_2$), in which a has a value from zero to two, inclusive, and L$_1$ and L$_2$ are independently selected from hydrogen and straight and branched alkyl and alkylaryl groups containing up to 18 carbon atoms, provided that L$_1$ and L$_2$ are not both hydrogen,

20 and R_5 and R_6 are each independently selected from hydrogen and straight or branched alkyl groups having up to 18 carbon atoms. R_4 is (-CH$_2$-)$_b$, wherein b independently has a value between zero and eight, inclusive; and R_2 is selected from straight and branched alkyl and alkylaryl groups containing up to 18 carbon atoms. At least one of R_2, R_5, R_6 and, when R_3 is -CHNL$_1$L$_2$, L$_1$ or L$_2$, contains at

25 least one ether linkage. The preferred species of R_2,R_3,R_4, R_5, R_6, a and b are the same as described above with respect to the poly(amide esters) of the present invention. In preferred dihydroxy monomer compounds, only R_2 contains an ether linkage.

        A basic requirement is to prepare a large enough *amount* of each

30 polymer with sufficiently high molecular weight to establish basic structure-

property correlations. However, because a large *number* of polymers are required for this methodology, there are practical requirements for practicing this methodology that the prior art does not address. First, easily purified monomers are preferred that have comparable reactivities at the polymerizable functionality

5 so the same polymerization conditions can be used to prepare the entire library. Secondly, in order to routinely construct polymer libraries, the potential for automating the entire process is also of considerable importance. Thus, it is necessary to use mild, reproducible polymerization conditions adaptable to small scale reactions and from which the isolation and purification procedures are

10 identical for each polymer. In order to reinforce the potential for automation, the process of isolation and purification should be designed so the individual polymers are never removed from the reaction vessel.

As noted above, the polyarylate copolymers are intended for use in medical applications. A fundamental result of the inventive methodology is that

15 more meaningful biological correlations are derived. *In vitro* correlations between polymer structure and the proliferative response of rat lung fibroblasts were established. Although cell response screening studies of biomedical polymers have been conducted in the past, the lack of common structural features among test materials prevented the identification of correlations between chemical structure

20 and cellular response. Because the polyarylate copolymers exhibited systematic variations in structure while sharing a range of common properties it was possible to correlate biological response with defined changes in the chemical structure of the tested polymers. This is a widely used approach in the pharmaceutical industry for the development of small molecule drugs, however the prior art does

25 not address this issue with respect to the development of degradable polymeric biomaterials.

Traditionally, the biomaterial field has relied on the availability of commodity polymers rather than polymers specifically used for medical applications. This particular utility of the inventive methodology is not in the

30 prior art associated with biomaterials development.

While specific properties that varied as a function of structural modifications have been described for the polyarylate copolymers, several

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properties remain essentially the same. In terms of processibility, all the polymers were soluble in common organic solvents and could be spin coated onto glass. Several test polymers were fabricated into solvent cast films, compression molded films, and extruded rods and ribbons. All 112 polymers appeared to be

5   amorphous. The structural modifications imparted to the 112 polymers did not involve changing the hydrolytically labile moieties. While the relative hydrolytic rate of these moieties might vary, the rate differences are not expected to be great. Water uptake studies and preliminary degradation studies suggest similar amounts of water are imbibed into films fabricated from several of the library polymers

10   with little only small differences in the rate of degradation. Finally, studies also strongly suggest that the tyrosine-derived polyarylates are biocompatible.

The inventive methodology produced a library which facilitates the selection of polymers for biomedical applications in ways not previously possible in the prior art. For example, polymers with an air-water contact angle around

15   70° often lead to optimum cell attachment and proliferation. From this polymer library it is possible to choose polymers of similar structure having a 70° contact angle that span a wide T_g range, including polymers that would be either glassy or rubbery at body temperature. In other subgroups of polymers, the glass transition can be kept constant while the air-water contact angle can be varied over a wide

20   range.

The following non-limiting examples set forth hereinbelow illustrate certain aspects of the invention. All parts and percentages are by mole percent unless otherwise noted, and all temperatures are in degrees Celsius. All solvents were HPLC grade. All other reagents were of analytical grade and were used as

25   received.

EXAMPLES

EXAMPLE 1: MONOMER SYNTHESIS

Tyrosine alkyl esters were coupled with recrystallized

30   3-(4-hydroxyphenyl)-propionic acid (or in some cases, 4-hydroxyphenylacetic acid) using EDCI (1.0 eq.) and HOBt (0.1 eq.) in a solution of either

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N-methylpyrrolidinone-ethyl acetate (1:3; 1.5M concentration in tyrosine ester) or acetonitrile (0.75M concentration in tyrosine ester). After aqueous workup, the desaminotyrosyl-tyrosyl diols **1** were obtained in purities up to 99% (HPLC) and 98% (DSC). Most of the diacids **2** were commercially available in at least 99%

5   purity. Less pure diacids **2** were recrystallized.

EXAMPLE 2: LIBRARY POLYMER SYNTHESIS

Small scale polymerizations were conducted and worked up entirely in tared 20 mL glass chromatography vials with PTFE lined caps. Careful

10   weighing of one equivalent each of the diacid **2** and desaminotyrosyl-tyrosyl diol **1** was necessary to ensure that high molecular weight material was isolated. First the diacid was weighed directly in the vial to minimize mass transfer weighing errors. Enough diacid **2** was used so one equivalent of desaminotyrosyl-tyrosyl diol **1** typically weighing in the range between 0.20-0.25g could then be added to

15   the vial. Dimethylaminopyridinium-p-toluenesulfonate (0.06-0.08g), methylene chloride (4 mL), and diisopropyl-carbodiimide (0.35 mL) were then sequentially added to the vial which was tightly capped and Parafilmed. The vials were transferred to a Labline water bath shaker (model 3540) and agitated (250 rpm) at $30 \pm 1°$ C for 36-48h. Work-up consisted of diluting each vial reaction mixture

20   with 16 mL methanol, recapping the vial, and vigorously shaking to precipitate the polymer **3**, then decanting the supernatant leaving the polymer in the vial. The polymer was then dissolved in methylene chloride (1-2 mL) followed by the addition of methanol (18 mL), vigorous shaking to re-precipitate the polymer, and decanting the supernatant. Methanol (5 mL) was added to the vial and decanted as

25   a final rinse. The polymer **3** was dried at ambient temperature in vacuum for 1 day then in vacuum at 45° C for one day.

EXAMPLE 3: POLYMER SYNTHESIS-LABORATORY SCALE (5-50g)

An equimolar amount of desaminotyrosyl-tyrosyl diol **1** and diacid **2**

30   were dissolved in methylene chloride to a concentration of 1.4 molar (in diol) in a 1 liter single-neck round bottom flask under nitrogen atmosphere. To this solution

was added dimethyl aminopyridinium-p-toluenesulfonate (0.4 eq.) followed by the syringe addition of diisopropyl carbodiimide (2.5 eq.) after which the reaction generally became clear. After about 1 hour a precipitate became evident. The reaction was stirred for 24-36 hours and then was transferred to a separatory

5   funnel and slowly added to a stirred (mechanical stirrer) solution of methanol (at least 10 volumes) to precipitate the polymer **3**. The supernatant was decanted and the polymer transferred to a separatory funnel, dissolved into methylene chloride (8-10% w/v), and precipitated into either methanol or isopropanol (10 volumes). Again the supernatant was decanted and then the polymer rinsed in methanol (or

10 isopropanol). The polymer **3** was then dried in vacuum at ambient temperature for 2-3 days then in vacuum at 45° C for 2 days.

MOLECULAR WEIGHT DETERMINATION

The gel permeation chromatographic system consisted of either a

15 Perkin Elmer pump model 250 or a Waters pump model 510, a Waters refractive index detector model 410, and either two PL-gel GPC columns (pore size 10^5 and 10^3 Å) or two Waters Styragel 7.8x300 mm GPC (HR3 and HR4) columns operated in series at a flow rate of 1 mL/min in THF. Molecular weights were calculated relative to polystyrene standards without further correction using Waters

20 Millenium Chromatography Manager software on a Digital VenturisFP model 466 personal computer. Samples (5 mg/mL) were filtered (PTFE, 0.45 mL syringe filter) prior to injection.

Molecular weights and polydispersities for the library of polyarylates are shown in Table II.

25

TABLE II

MOLECULAR WEIGHTS ($Mw = 10^3$)

AND POLYDISPERSITIES FOR THE LIBRARY OF POLYARYLATES

		Succinic Acid	Glutaric Acid	Diglycolic Acid	Adipic Acid	3-Methyl-Adipic Acid	Suberic Acid	Dioxaoctane-dioic Acid	Sebacic Acid
5	DTM	61	76	11	77	100	44	18	113
		1.40	1.84	1.50	1.53	1.68	1.69	1.66	1.45
	DTE	79	49	20	129	84	237	22	57
		1.62	1.68	1.49	1.36	1.48	1.50	1.32	1.89
	DTB	81	63	26	142	58	123	25	112
		2.23	1.64	1.54	1.80	1.61	1.88	1.50	1.87
	DTH	79	67	26	61	61	161	38	82
		1.48	1.59	1.45	1.46	1.59	1.39	1.76	1.43
10	DTO	67	83	35	68	95	134	28	68
		1.62	2.10	1.80	1.84	1.76	1.79	1.89	1.68
	DTD	112	113	35	137	164	117	61	189
		1.46	1.49	1.45	1.44	1.34	1.48	2.09	1.45
	DTG	65	102	21	106	71	45	45	78
		1.80	1.71	1.50	1.75	1.60	1.68	1.96	1.71
	DTiP	78	89	31	32	58	33	36	88
		2.64	2.93	1.74	1.47	1.64	1.54	1.96	1.66
15	DTiB	81	99	20	135	72	203	57	44
		1.67	1.56	1.51	1.62	1.93	1.49	1.55	1.48
	DTsB	72	127	21	83	89	133	25	185
		2.08	1.89	1.57	1.94	1.82	2.24	1.73	1.77
20	DTBn	70	98	24	122	101	43	41	117
		1.45	1.33	1.64	1.44	1.42	1.39	1.42	1.36
	THE	37	28	14	66	49	119	19	158
		1.73	1.77	1.49	1.58	1.82	1.39	1.47	1.74
	HTH	46	51	17	54	74	103	42	134
		1.70	1.70	1.64	1.57	1.91	1.57	1.81	2.03
	HTO	68	29	35	101	47	36	29	44
		1.95	1.93	1.62	1.76	1.94	1.87	1.65	1.84

THERMAL ANALYSIS/DIFFERENTIAL SCANNING CALORIMETRY (DSC):

A thermal analyzer model DSC 910 (TA Instruments, Delaware) calibrated with indium was used to determine polymer glass transition (T_g) temperatures and monomer absolute purities. For T_g measurement, each

5   specimen was subjected to two consecutive DSC scans with a heating rate of 10°C min^{-1}. After the first run to 50°C above T_g the specimen was quenched with liquid nitrogen to at least 50°C below T_g and the second scan was immediately obtained from which the T_g was determined by the midpoint on the endothermic changes associated with the glass transition. The reproducibility of the T_g measurement

10   was within 1°C for different specimens and polymer batches. Monomer purity was measured by heating a previously dried (50°C in vacuum) sample (2-3 mg) at a rate of 10°C min^{-1} until the temperature was ca. 20°C below the melting point and then the heating rate reduced to 1°C min^{-1} until the temperature reaches about 10°C above the melting point. After this heating cycle, the purity and depression

15   were determined.

T_g values for the library of polyarylates are shown in Table III.

TABLE III

T_g Values For The Library Of Polyarylates

	Succinate (1)	Diglycolate (2)	Glutarate (3)	Adipate (4)	3-Methyl Adipate (5)	Dioxaoctane-dioate (6)	Suberate (7)	Sebacate (8)
DTM (1')	91	82	76	69	68	63	55	47
DTiP (2')	82	80	68	58	54	58	46	44
DTE (3')	78	79	69	61	63	53	50	44
DTBn (4')	78	76	66	61	60	55	47	42
HTB (5')	73	66	65	65	63	50	54	43
DTiB (6')	75	72	62	56	47	50	42	33

DTsB (7')	75	68	58	50	56	44	46	36
DTB (8')	67	64	55	46	45	45	37	30
HTH (9')	59	46	42	32	38	31	27	23
DTH (10')	53	45	43	38	33	28	27	20
HTO (11')	51	51	38	28	30	23	22	16
DTO (12')	48	40	32	28	30	16	21	13
DTD (13')	40	36	28	22	19	17	15	12
DTG (14')	34	27	21	15	16	18	6	2

THERMAL ANALYSIS/THERMOGRAVIMETRIC ANALYSIS (TGA):

The decomposition temperature (Td) was determined by thermogravimetric analysis on a TGA 951 (TA Instruments, Delaware) and was reported at 10% decrease in weight. The heating rate was 10°C min^{-1} and the average sample size was 30 mg.

CONTACT ANGLE MEASUREMENT

Air-water contact angles were measured on a Rame-Hart goniometer model 100-00-115 using double distilled water as the probe. The water was deposited onto the polyarylate spin coated glass cover slip in a small volume from above forming a sessile drop having a diameter of approximately 2.5 mm. Results were the average of at least 5 measurements (error ± 1°).

Contact angle values for the library of polyarylates are shown in Table IV:

TABLE IV

CONTACT ANGLE VALUES FOR THE LIBRARY OF POLYARYLATES

	Sebacate (1)	Suberate (2)	3-Methyl Adipate (3)	Adipate (4)	Glutarate (5)	Dioxaoctane-dioate (6)	Succinate (7)	Diglycolate (8)
DTD (1')	101.2	95.5	94.0	96.7	95.6	94.4	96.1	97.5
HTO (2')	90.7	89.5	88.4	89.9	87.7	90.4	86.6	86.9
DTO (3')	94.6	88.1	86.3	87.3	85.7	88.1	86.8	86.6
HTH (4')	86.6	85.6	82.9	84.2	83.3	83.1	81.8	80.8
DTH (5')	90.3	84.4	83.8	83.7	79.9	81.0	81.0	80.5
DTG (6')	86	85.7	78.6	79.1	75.6	75.9	70.3	70.1
DTiB (7')	82.5	79.7	76.8	76.9	76.3	73.7	74.8	73.9
DTsB (8')	82.1	78.7	76.4	75.9	74.0	73.5	73.7	73.1
DTB (9')	83.6	81.3	78.7	77.6	74.9	75.2	74.0	72.5
DTBn (10')	80.7	77.1	75.3	74.1	73.8	71.1	72.6	71.1
DTiP (11')	81.4	77.0	75.3	73.5	71.8	69.6	70.7	67.9
DTB (12')	79.5	75.9	75.3	73.0	69.0	68.5	68.7	67.3
THE (13')	77.0	74.8	72.7	71.4	70.7	67.7	68.1	66.3
DTM (14')	77.3	74.1	77.5	70.7	67.2	64.6	66.4	64.2

Glass cover slips (18 mm diameter) were sequentially sonicated twice each in solutions of 25% NaOH (10 minutes), 25% HCl (10 minutes), and 2% Micro detergent (30 minutes). The cover slips were thoroughly rinsed after each sonication

5 with distilled deionized water and after the final rinse sequentially sonicated twice each in absolute ethanol (5 minutes) and then methylene chloride (5 minutes). The cover slips were then stored in a solution of methylene chloride until needed for spin coating and were carefully handled either with tweezers or on the edge by hand while wearing latex disposable gloves. Each polyarylate solution was prepared by first adding about

10 20-30 mg of polymer to a tared glass vial and adding enough methylene chloride to give a 2.5% (w/v) solution which was then filtered (PTFE syringe filter, 0.45 mm). Cover slips were removed from the methylene chloride solution and spun dried. Polymer solution was added to provide complete coverage of the glass surface which was then spun for 20 seconds at 2000 rpm. The procedure was repeated twice more

15 to ensure a smooth surface and then the cover slips were placed into individual disposable petri dishes and dried at ambient temperature in vacuum prior to contact angle measurement.

SPIN COATED GLASS COVER SLIP PREPARATION FOR CELL
20 ## PROLIFERATION ASSAYS.

Glass cover slips (15 mm diameter) were cleaned in the same way as were the cover slips used for contact angle measurement. After the final sonication in methylene chloride, the cover slips were rinsed twice in ethyl acetate and then sonicated twice (5 minutes) in a 2.5% (w/v) poly(styrene-silane) copolymer-ethyl

25 acetate solution. The cover slips were soaked in this solution a further 10 minutes, then placed flat one cover slip high in glass petri dishes, and stored in an oven at 60°C in vacuum for 2 days. After cooling to ambient temperature, the cover slips were removed from the vacuum oven and rinsed in ethyl acetate (2x) and methanol (2x), and then ethyl acetate once more before drying on crumbled aluminum foil in air for

30 30 minutes. The cover slips were then stored in a glass vial until needed for spin coating. Filtered (PTFE syringe filter, 0.45 mm) 2.5%(w/v) polyarylate-methylene

chloride solutions were used to spin coat each glass cover slip two times to ensure a smooth surface. The polymer solution was added to provide complete coverage of the glass surface which was then spun for 20 seconds at 2000 rpm. The cover slips were handled either with tweezers or on the edge by hand while wearing latex disposable

5   gloves and carefully placed into individual wells in non-tissue culture treated 24-well cell culture plates which were then stored at ambient temperature in vacuum until needed for use.

CELLULAR PROLIFERATION ASSAY

10   Glass coverslips previously spin coated with each of the polymers, were placed in 24 well, non-tissue culture treated polystyrene plates. Four glass coverslips for each polymer (n = 4) were used in each assay and tissue culture polystyrene served as the control material. Employing a drop culture technique, 1×10^4 cells/cm^2 in DMEM media supplemented with 10% heat inactivated fetal

15   bovine serum were seeded onto each surface and incubated for one hour. Following the one hour attachment period, the wells in each plate were washed with PBS to remove non-adherent cells, replenished with media, and returned to the incubator. The number of fibroblasts present on each of the surfaces was measured at seven days with the commercially available MTS colormetric assay

20   (Promega, Madison, WI).

The foregoing examples illustrate how the present invention may be employed to establish a correlation between chemical structure and T_g, fibroblast proliferation, and air-water contact angles.

The characterization data for desaminotyrosyl-tyrosine diols not

25   previously reported in the literature is set forth below. All diols are variations of the general structure of Fig. 3.

L-Tyrosine-N-{3-(4-hydroxyphenyl)-1-oxopropyl}-Methyl Ester, DTM

n=2, R$_2$= CH$_3$-

30   (C$_{19}$H$_{21}$NO$_5$)

Molecular Weight, 343.39.

Melting Point (C°) 123-124.

^{1}H-NMR (200 MHz, DMSO) δ 9.25 (s, 1 H, phenol), 9.16 (s, 1 H, phenol), 8.27 (d, 1 H, amide), 6.96 (m, 4 H, aryl), 6.67 (d, 4 H, aryl), 4.40 (q, 1 H, a-proton), 3.59 (s, 3 H, -O-CH$_3$), 2.60-2.92 (m, 4 H, -CH$_2$-), 2.33 (t, 2 H, -CH$_2$-).

^{13}C-NMR (50 MHz, DMSO) δ 172.5, 171.9, 156.2, 155.6, 131.5, 130.2, 129.2, 127.5, 115.2, 54.1, 51.9, 37.3, 36.3, 30.4.

Anal. Calcd.: C, 66.46; H, 6.17; N, 4.08. Found: C, 66.39; H, 6.26; N, 3.97.

L-Tyrosine-N-{3-(4-hydroxyphenyl)-1-oxopropyl} -Dodecyl Ester, DTD

n=2, R$_2$= CH$_3$ (CH$_2$)$_{11}$-

C$_{30}$H$_{43}$NO$_5$

Molecular Weight, 497.68.

Melting Point (C°) 93-94.

^{1}H-NMR (200 MHz, DMSO) δ 9.23 (s, 1 H, phenol), 9.14 (s, 1 H, phenol), 8.25 (d, 1 H, amide), 6.96 (m, 4 H, aryl), 6.65 (d, 4 H, aryl), 4.38 (q, 1 H, a-proton), 3.59 (t, 2 H, -O-CH$_2$-), 2.60-2.86 (m, 4 H, -CH$_2$-), 2.32 (t, 2 H, -CH$_2$-), 1.49 (bs, 2 H, [O-CH$_2$-]CH$_2$-), 1.24 (s, 18 H, -CH$_2$-), 0.86 (bs, 3 H, -CH$_3$).

^{13}C-NMR (50 MHz, DMSO) δ 172.0, 171.8, 156.3, 155.7, 131.4, 130.2, 129.2, 127.4, 115.2, 64.2, 54.2, 37.3, 36.4, 31.6, 30.5, 29.3, 29.0, 28.9, 28.3, 25.5, 22.4, 14.2.

Anal. Calcd.: C, 72.40; H, 8.71; N, 2.82. Found: C, 71.88; H, 8.58; N, 2.71.

L-Tyrosine-N-{ 3-(4-hydroxyphenyl)-1-oxopropyl} -Isopropyl Ester, DTiP

n=2, R$_2$= (CH$_3$)$_2$CH-

C$_{21}$H$_{25}$NO$_5$

Molecular Weight, 371.44.

Melting Point (C°) 79 (DSC).

^{1}H-NMR (200 MHz, DMSO) δ 9.24 (s, 1 H, phenol), 9.15 (s, 1 H, phenol), 8.22 (d, 1 H, amide), 6.96 (m, 4 H, aryl), 6.67 (d, 4 H, aryl), 4.84 (quint., 1 H, [O-(CH$_3$)$_2$]-H), 4.33 (q, 1 H, a-proton), 2.82 (t, 2 H, -CH$_2$-), 2.65 (t, 2 H, -CH$_2$-), 2.33 (t, 2 H, -CH$_2$-), 1.16 (d, 3 H, -CH$_3$), 1.06 (d, 3 H, -CH$_3$).

^{13}C-NMR (50 MHz, DMSO) δ 171.8, 171.5, 156.2, 155.7, 131.5, 130.3, 129.2, 127.4, 115.2, 68.0, 54.3, 37.3, 36.4, 30.4, 21.8, 21.6.

Anal. Calcd.: C, 67.91; H, 6.78; N, 3.77. Found: C, 67.61; H, 7.19; N, 3.54.

L-Tyrosine-N-{3-(4-hydroxyphenyl)-1-oxopropyl} -Isobutyl Ester, DTiB

n=2, R$_1$= (CH$_3$)$_2$CH-CH$_2$-

C$_{22}$H$_{25}$NO$_5$

Molecular Weight, 385.46.

Melting Point (C°) 104.6 (DSC).

^{1}H-NMR (200 MHz, DMSO) δ 9.23 (s, 1 H, phenol), 9.15 (s, 1 H, phenol), 8.26 (d, 1 H, amide), 6.98 (m, 4 H, aryl), 6.65 (d, 4 H, aryl), 4.38 (q, 1 H, a-proton), 3.78 (d, 2 H, -O-CH$_2$-), 2.60-2.87(m, 4 H, -CH$_2$-), 2.32 (t, 2 H, -CH$_2$-), 1.81 (m, 1 H, [(-O-CH$_2$)C(CH$_3$)$_2$-]H), 1.76 (d, 6 H, -CH$_3$).

^{13}C-NMR (50 MHz, DMSO) δ 172.1, 171.8, 156.2, 155.6, 131.5, 130.2, 129.2, 127.5, 115.3, 70.3, 54.3, 37.3, 36.4, 30.4, 27.5, 19.0.

Anal. Calcd.: C, 68.55; H, 7.06; N, 3.63. Found: C, 68.60; H, 7.21; N, 3.55.

L-Tyrosine-N-{3-(4-hydroxyphenyl)-1-oxopropyl} -*sec*-Butyl Ester, DTsB

n=2, R$_2$= CH$_3$CH$_2$CH(CH$_3$)-

C$_{22}$H$_{27}$NO$_5$

Molecular Weight, 385.46.

Melting Point (C°) 121 (DSC).

^{1}H-NMR (200 MHz, DMSO) δ 9.24 (s, 1 H, phenol), 9.15 (s, 1 H, phenol), 8.24 (d, 1 H, amide), 6.98 (m, 4 H, aryl), 6.67 (d, 4 H, aryl), 4.70

(m, 1 H, -O[(-CH$_2$)C(CH$_3$-)]H), 4.35 (q, 1 H, a-proton), 2.60-2.90 (m, 4 H, -CH$_2$-), 2.32 (t, 2 H, -CH$_2$-), 1.45 (m, 2 H, -CH$_2$-), 1.08 (d 3 H, -CH$_3$), 0.80 (dt, 3 H, -CH$_3$).

^{13}C-NMR (50 MHz, DMSO) δ 171.9, 171.8, 156.2, 155.7, 131.5, 130.3, 129.3, 127.4, 115.2, 72.5, 72.3, 54.4, 54.3, 37.3, 36.4, 30.4, 28.4, 28.3, 19.4, 19.3, 9.6.

Anal. Calcd.: C, 68.55; H, 7.06; N, 3.63. Found: C, 68.35; H, 7.18; N, 3.59.

L-Tyrosine-N-{3-(4-hydroxyphenyl)-1-oxopropyl} -Benzyl Ester, DTBn

n = 2, R$_2$ = -CH$_2$C$_6$H$_5$

C$_{25}$H$_{25}$NO$_5$

Molecular Weight, 419.49.

Melting Point (C°) 113-115.

1H-NMR (200 MHz, DMSO) δ 9.25 (s, 1 H, phenol), 9.16 (s, 1 H, phenol), 8.31 (d, 1 H, amide), 7.30 (m, 5 H, aryl), 6.97 (m, 4 H, aryl), 6.65 (d, 4 H, aryl), 5.07 (s, 2 H, Ph-CH$_2$-), 4.44 (q, 1 H, a-proton), 2.59-2.89 (m, 4 H, -CH$_2$-), 2.32 (t, 2 H, -CH$_2$-).

^{13}C-NMR (50 MHz, DMSO) δ 171.9,156.3, 155.7, 136.1, 131.5, 130.3, 129.2, 128.6, 128.3, 128.1, 127.3, 115.3, 66.1, 54.3, 37.3, 36.3, 30.4

Anal. Calcd.: C, 71.58; H, 6.01; N, 3.34. Found: C, 71.14; H, 6.31; N, 3.16.

L-Tyrosine-N-{2-(4-hydroxyphenyl)-1-oxoethyl} -Ethyl Ester, THE

n = 1, R$_2$ = CH$_3$CH$_2$-

C$_{19}$H$_{21}$NO$_5$

Molecular Weight, 343.39.

Melting Point (C°) 124-125.

^{1}H-NMR (200 MHz, DMSO) δ 9.25 (s, 2 H, phenol), 8.37 (d, 1 H, amide), 6.97 (t, 4 H, aryl), 6.67 (d, 4 H, aryl), 4.35 (q, 1 H, a-proton), 4.05 (q, 2 H, -O-CH$_2$-), 3.31 (s, 2 H, Ph-CH$_2$-), 2.86 (m, 2 H, -CH$_2$-), 1.12 (t, 3 H, -CH$_3$).

^{13}C-NMR (50 MHz, DMSO) δ 171.9, 170.9, 156.3, 156.0, 130.3, 130.1, 127.4, 126.4, 115.2, 115.1, 60.7, 54.2, 41.3, 36.3, 14.2.

Anal. Calcd.: C, 66.46; H, 6.17; N, 4.08. Found: C, 66.41; H, 6.31; N, 4.03.

5

L-Tyrosine-N-{2-(4-hydroxyphenyl)-1-oxoethyl} -Hexyl Ester, HTH

n = 1, $R_2 =$ CH$_3$(CH$_2$)$_5$-

C$_{23}$H$_{29}$NO$_5$

Molecular Weight, 399.50.

10   Melting Point (C°) 106-108.

^{1}H-NMR (200 MHz, CDCL3) δ 7.73 (bs, 1 H, phenol), 7.59 (bs, 1 H, phenol), 6.91 (d, 2 H, aryl), 6.64 (d, 6 H, aryl), 6.07 (d, 1 H, amide), 4.78 (q, 1 H, a-proton), 4.12 (t, 2 H, -O-CH$_2$-), 3.46 (s, 2 H, Ph-CH$_2$-), 2.93 (m, 2 H, -CH$_2$-), 1.62 (m, 2 H, -CH$_2$-),   1.28 (bs, 6 H, -CH$_2$-), 0.87 (bs, 3 H, -

15 CH$_3$).

^{13}C-NMR (50 MHz, CDCl$_3$) δ 173.2, 172.6, 156.1, 155.8, 131.2, 130.6, 126.8, 125.6, 116.6, 116.2, 66.7, 53.6, 43.0, 37.1, 31.8, 28.9, 25.9, 22.9, 14.5.

Anal. Calcd.: C, 69.15; H, 7.32; N, 3.51. Found: C, 69.13; H,

20 7.33; N,3.44.

L-Tyrosine-N-{2-(4-hydroxyphenyl)-1-oxoethyl} -Octyl Ester, HTO

n = 1, $R_2 =$ CH$_3$(CH$_2$)$_7$-

C$_{25}$H$_{33}$NO$_5$

25   Molecular Weight, 427.55.

Melting Point (C°) 59-61.

^{1}H-NMR (200 MHz, CDCL3) δ 7.60 (bs, 2 H, phenol), 6.90 (d, 2 H, aryl), 6.67 (d, 6 H, aryl), 6.07 (d, 1 H, amide), 4.79 (q, 1 H, a-proton), 4.14 (t, 2 H, -O-CH$_2$-), 3.46 (s, 2 H, Ph-CH$_2$-), 2.93 (m, 2 H, -CH$_2$-), 1.63

30 (bs, 2 H, -CH$_2$-), 1.26 (s, 10 H, -CH$_2$-), 0.86 (bs, 3 H, -CH$_3$).

^{13}C-NMR (50 MHz, CDCl$_3$) δ 173.2, 172.6, 156.1, 155.8, 131.2, 130.6, 126.8, 125.7, 116.6, 116.3, 66.7, 53.6, 43.0, 37.1, 32.2, 29.6, 28.9, 26.3, 23.1, 14.6.

Anal. Calcd.: C, 70.23; H, 7.78; N, 3.28. Found: C, 69.94; H,
5 7.46; N, 3.16.

L-Tyrosine-N-{3-(4-hydroxyphenyl)-1-oxopropyl}-{2-(2-ethoxyethoxy)ethyl}Ester, DTG

n=2, R$_2$= CH$_3$CH$_2$O-CH$_2$CH$_2$O-CH$_2$CH$_2$-

C$_{24}$H$_{31}$NO$_7$

10   Molecular Weight, 445.53

Melting Point (°C), oil at ambient temperature.

^{1}H-NMR (200 MHz,CDCl$_3$) δ 7.62-7.50 (bs, 2 H, phenol), 6.88 (d, 2H, aryl), 6.70 (q, 6 H, aryl), 6.34 (d, 1 H, amide), 4.78 (q. 1 H, a-proton), 4.17 (bs, 2 H, -O-CH$_2$-), 3.60 (bs, 6 H, -CH$_2$-O-CH$_2$-O-), 3.51 (q. 2 H, -O-CH$_2$-
15 Methyl), 2.90 (m, 2 H, -CH$_2$-), 2.76 (m, 2 H, -CH$_2$-), 2.37 (m, 2 H, -CH$_2$ -), 1.16 (t, 3 H, -CH$_3$)

^{13}C-NMR (50 Mhz. CDCl$_3$) δ 173.5, 172.2, 155.8, 155.1, 132.1, 130.8, 129.8, 127.3, 116.0, 70.9, 70.1, 69.2, 67.3, 53.9, 38.7, 37.3, 31.1, 15.5.

Anal. Calcd.: C, 64.70; H, 7.01; N, 3.14. Found: C, 64.88; H,
20 6.79; N, 3.03.

L-Tyrosine-n-[3-(4-hydroxypheny)-1-oxopropyl]-[2-(2-ethoxyethoxy) ethyl]ester DTG

C$_{24}$H$_{31}$NO$_7$

Molecular Weight, 445.53

25   Melting Point (C°) Boil at ambient temperature.

^{1}H-NMR (200 MHz, CDCl$_3$) δ 7.62-7.50 (bs, 2 H, phenol), 6.88(d, 2 H aryl, 6.70(q, 6 H, aryl), 6.34(d, 1 H, amide), 4.78(q, 1 H, α-proton), 4.17(bs, 2 H, -O-CH$_2$-), 3.60(bs, 6 H, -CH$_2$-O-CH$_2$-CH$_2$-O-), 3.51(q, 2 H, -O-CH$_2$-CH$_3$), 2.90(m, 2 H, -CH$_2$-), 2.76(m, 2 H, -CH$_2$-), 2.37(m, 2 H, -CH$_2$-), 1.16(t, 3 H, -
30 CH$_3$).

^{13}C-NMR (50 MHz, CDCl$_3$) δ 173.5, 172.2, 155.8, 155.1, 132.1, 130.8, 129.8, 127.3, 116.0, 70.9, 70.1, 69.2, 67.3, 64.9, 53.9, 38.7, 37.3, 31.1, 15.5.

^{13}C-NMR (50 MHz, DMSO) δ 171.9, 156.2, 155.7, 131.5, 130.3,
5   129.2, 127.4, 115.2, 70.1, 69.4, 68.4, 65.8, 64.0, 54.2, 37.3, 36.3, 30.4, 15.3.

Anal. Calcd.: C, 64.707; H 7.01; N, 3.28. Found: C, 64.88; H, 6.79; N, 3.03.

The foregoing examples and description of the preferred embodiment should be taken as illustrating, rather than as limiting, the present invention as
10   defined by the claims. As will be readily appreciated, numerous variations and combinations of the features set forth above can be utilized without departing from the present invention as set forth in the claims. Such variations are not regarded as a departure from the spirit and scope of the invention, and all such variations are intended to be included within the scope of the following claims.

15

WHAT IS CLAIMED IS:

1.   A multidimensional copolymer array, comprising a plurality of copolymers polymerized from at least two independently variable sets of
5   monomers, wherein said polymerization is characterized by:

(a) selecting a first homologously varying series of monomers with non-varying polymerizable functional groups;

10   (b) selecting at least one additional homologously varying series of different monomers having non-varying polymerizable functional groups that are reactive with the polymerizable functional groups of said first series of monomers to form copolymers; and

15   (c) separately reacting a plurality of monomers from said first monomer series with a plurality of monomers from each of said additional monomer series to form said plurality of copolymers;

wherein said homologous variations of said monomer series are selected
20   to determine the effect of independently varying at least two different structural features of said copolymer on at least one end-use property of said copolymer.

2.   The copolymer array of claim 1, wherein said polymerization reaction is a free-radical process.
25

3.   The copolymer array of claim 2, wherein said free-radical process is an ionic polymerization.

4.   The copolymer array of claim 1, wherein said separate reactions
30   are performed in parallel.

5.   The copolymer array of claim 1, wherein said separate reactions are performed in solution.

6. The copolymer array of claim 1, wherein said separate reactions are performed in bulk.

7. The copolymer array of claim 1, wherein said separate reactions are performed in the presence of a catalyst.

8. The copolymer array of claim 1, wherein said separate reactions are performed in the absence of a catalyst.

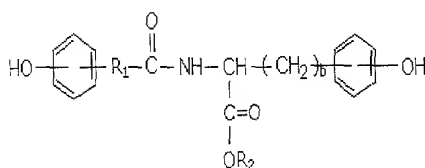9. The copolymer array of claim 1, wherein said copolymers are further modified by chemical reactions or cross-linking.

10. A multi-dimensional condensation-type copolymer array, comprising a plurality of copolymers polymerized from at least two independently variable sets of monomers, wherein said polymerization is characterized by:

(a) selecting a first homologously varying series of monomers with non-varying polymerizable functional groups;

(b) selecting at least one additional homologously varying series of different monomers having non-varying polymerizable functional groups that are reactive with the polymerizable functional groups of said first series of monomers to condense to form copolymers; and

(c) separately reacting a plurality of monomers from said first monomer series with a plurality of monomers from each of said additional monomer series to form said plurality of condensation-type copolymers;

wherein said homologous variations of said monomer series are selected to determine the effect of independently varying at least two different structural features of said copolymer on at least one end-use property of said copolymer.

11.   The copolymer array of claim 10, wherein said condensation-type reaction is an interfacial process.

12.   The copolymer array of claim 10, wherein said condensation-type reaction is a suspension process.

13.   The copolymer array of claim 10, wherein said separate reactions are performed in parallel.

14.   The copolymer array of claim 10, wherein said separate reactions are performed in solution.

15.   The copolymer array of claim 10, wherein said separate reactions are performed in bulk.

16.   The copolymer array of claim 10, wherein said separate reactions are performed in the presence of a catalyst.

17.   The copolymer array of claim 10, wherein said separate reactions are performed in the absence of a catalyst.

18.   The copolymer array of claim 10, wherein said polymerizable functional groups of said first monomer series are amine or hydroxyl groups and said polymerizable functional groups of said additional series of monomers are selected from the group consisting of carboxylic acids, esters, anhydrides and isocyanates.

19.   The copolymer array of claim 18, wherein said additional series of monomers comprise second and third monomer series, said second monomer series is selected from the group consisting of carboxylic acids, esters, anhydrides and isocyanates, and said third monomer series comprises a plurality of alkylene oxides selected from the group consisting of ethylene

oxide, propylene oxide, isopropylene oxide, butylene oxide, isobutylene oxide and random and block polymers and copolymers thereof.

20.   The copolymer array of claim 18, wherein said polymerizable functional groups of said first monomer series are hydroxyl groups and said additional monomer series comprise a monomer series with polymerizable carboxylic acid groups.

21.   The copolymer array of claim 20, wherein said first monomer series comprises a plurality of different diphenol compounds, each having the general structure:

$$HO \underset{}{-\!\!\left[\!\!\left[\bigcirc\right]\!\!\right]\!\!} R_1 - \overset{\overset{O}{\|}}{C} - NH - \underset{\underset{OR_2}{\overset{|}{C=O}}}{\overset{|}{CH}} -\!\!\left(CH_2\right)_b \!\!-\!\!\left[\!\!\left[\bigcirc\right]\!\!\right]\!\!- OH$$

wherein R_1 is selected from the group consisting of -CH=CH-, $(-CH_2-)_a$, and -CHN(L_1L_2), in which a has a value from zero to eight, inclusive, and L_1 and L_2 are independently selected from the group consisting of hydrogen and straight and branched alkyl and alkylaryl groups containing up to 18 carbon atoms, provided that L_1 and L_2 are not both hydrogen; b independently has a value between zero and eight, inclusive; and R_2 is selected from the group consisting of straight and branched alkyl and alkylaryl groups containing up to 18 carbon atoms.
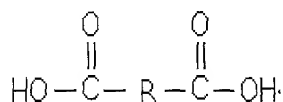
22.   The copolymer array of claim 20, wherein said first monomer series comprises a plurality of different aromatic-aliphatic dihydroxy compounds, each having the general structure:

$$HO - \underset{\underset{R_6}{\overset{|}{C}}}{\overset{\overset{R_5}{|}}{C}} - R_3 - \overset{\overset{O}{\|}}{C} - NH - \underset{\underset{OR_2}{\overset{|}{C=O}}}{\overset{|}{CH}} - R_4 -\!\!\left[\!\!\left[\bigcirc\right]\!\!\right]\!\!- OH$$

wherein R_3 is selected from the group consisting of -CH=CH-, $(-CH_2-)_a$, and -CHN(L_1L_2), in which a has a value from zero to eight, inclusive, and L_1 and L_2 are independently selected from the group consisting of hydrogen and straight and branched alkyl and alkylaryl groups containing up to 18 carbon

5 atoms, provided that L_1 and L_2 are not both hydrogen; R_5 and R_6 are each independently selected from the group consisting of hydrogen and straight or branched alkyl groups having up to 18 carbon atoms, R_4 is $(-CH_2-)_b$, wherein b independently has a value between zero and eight, inclusive; and R_2 is selected from the group consisting of straight and branched alkyl and alkylaryl groups

10 containing up to 18 carbon atoms.

23.   The copolymer array of claim 20, wherein said monomer series with polymerizable carboxylic acid groups comprises a plurality of different dicarboxylic acid compounds, each having the general structure:

15

$$HO - \overset{\overset{\displaystyle O}{\displaystyle \|}}{C} - R - \overset{\overset{\displaystyle O}{\displaystyle \|}}{C} - OH$$

wherein R is selected from the group consisting of saturated and unsaturated, substituted and unsubstituted alkyl, aryl and alkylaryl groups containing up to

20 18 carbon atoms.

24.   The copolymer array of claim 21, wherein for one or more of said monomers of said first monomer series, at least one of R_2, L_1 or L_2 contain at least one ether linkage.

25

25.   The copolymer array of claim 22, wherein for one or more of said monomers of said first monomer series, at least one of R_2, R_5, R_6, L_1 or L_2 contain at least one ether linkage.

30   26.   The copolymer array of claim 23, wherein for one or more of said monomers of said dicarboxylic acid monomer series, R contains at least one ether linkage.

27.   The copolymer array of claim 10, wherein said copolymers are further modified by chemical reactions or cross-linking.

28.   A method for determining the effect of independently varying at least two different structural features of a copolymer on at least one end-use property of said copolymer, comprising:

(a)   measuring at least one end-use property of each copolymer of said copolymer array of claim 1; and

(b)   comparing the variations in each end-use property measured for each of said copolymers as a function of the homologous variation within said monomer series from which said copolymers were polymerized to determine any relationship between said homologous variations and said end-use property variations among said copolymers;

thereby identifying specific members of said plurality of copolymers having useful properties for specific end-uses.

29.   The method of claim 28, wherein said polymerization reaction is a free-radical process.

30.   The method of claim 29, wherein said free-radical process is an ionic polymerization.

31.   The method of claim 28, wherein said separate reactions are performed in parallel.

32.   The method of claim 28, wherein said separate reactions are performed in solution.

33.   The method of claim 28, wherein said separate reactions are performed in bulk.

34.   The method of claim 28, wherein said separate reactions are
5   performed in the presence of a catalyst.

35.   The method of claim 28, wherein said separate reactions are performed in the absence of a catalyst.

10   36.   The method of claim 28, wherein said copolymers are further modified by chemical reactions or cross-linking.

37.   The method of claim 28, wherein said end-use properties are measured by ELISA, SAM, chromatographic methods, DSC, TGA, DMA,
15   TMA, microscopic techniques or processing methods.

38.   The method of claim 28, wherein the end-use property that is measured is a mechanical property, a viscoelastic property, a morphological property, an electrical property, an optical property, solute or gas permeability,
20   surface tension or a thermal property.

39.   The method of claim 28, wherein the end-use property that is measured is antibacterial activity, blood compatibility, tissue compatibility, drug release characteristics, biological interactions with living organisms,
25   hydrolytic degradation or protein adsorption characteristics.

40.   The method of claim 28, wherein the end-use property that is measured is polymer processability, radiation stability, sterilizability, adhesive properties, hydrophobic characteristics or stability to specific reaction
30   conditions.

41.   A method for determining the effect of independently varying at least two different structural features of a condensation-type copolymer on at least one end-use property of said copolymer, comprising:

5   (a)   measuring at least one end-use property of each copolymer of said copolymer array of claim 10; and

        (b)   comparing the variations in each end-use property measured for each of said copolymers as a function of the homologous variation within said 10 monomer series from which said copolymers were polymerized to determine any relationship between said homologous variations and said end-use property variations among said copolymers;

        thereby identifying specific members of said plurality of copolymers 15 having useful properties for specific end-uses.

        42.   The method of claim 41, wherein said condensation-type copolymers are prepared by an interfacial process.

20   43.   The method of claim 41, wherein said condensation-type copolymers are prepared by a suspension process.

        44.   The method of claim 41, wherein said condensation-type copolymers are synthesized in parallel.

25

        45.   The method of claim 41, wherein said condensation-type copolymers are polymerized in solution.

        46.   The method of claim 41, wherein said condensation-type 30 copolymers are polymerized in bulk.

47.   The method of claim 41, wherein said condensation-type copolymers are polymerized in the presence of a catalyst.

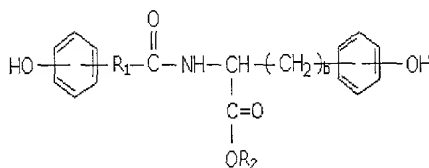48.   The method of claim 41, wherein said condensation-type copolymers are polymerized in the absence of a catalyst.

49.   The method of claim 41, wherein said polymerizable functional groups of said first monomer series are amine or hydroxyl groups and said polymerizable functional groups of said additional series of monomers are selected from the group consisting of carboxylic acids, esters, anhydrides and isocyanates.

50.   The method of claim 49, wherein said additional series of monomers comprise second and third monomer series, said second monomer series is selected from the group consisting of carboxylic acids, esters, anhydrides and isocyanates, and said third monomer series comprises a plurality of alkylene oxides selected from the group consisting of ethylene oxide, propylene oxide, isopropylene oxide, butylene oxide, isobutylene oxide and random and block polymers and copolymers thereof.

51.   The method of claim 49, wherein said polymerizable functional groups of said first monomer series are hydroxyl groups and said additional monomer series comprise a monomer series with polymerizable carboxylic acid groups.
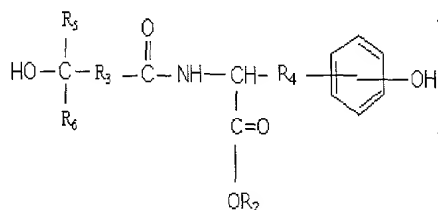
52.   The method of claim 51, wherein said first monomer series comprises a plurality of different diphenol compounds, each having the general structure:
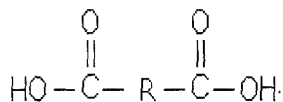
wherein R_1 is selected from the group consisting of -CH=CH-, $(-CH_2-)_a$, and
-CHN(L$_1$L$_2$), in which a has a value from zero to eight, inclusive, and L$_1$ and
L$_2$ are independently selected from the group consisting of hydrogen and
straight and branched alkyl and alkylaryl groups containing up to 18 carbon
5   atoms, provided that L$_1$ and L$_2$ are not both hydrogen; b independently has a
value between zero and eight, inclusive; and R$_2$ is selected from the group
consisting of straight and branched alkyl and alkylaryl groups containing up to
18 carbon atoms.

10   53.   The method of claim 51, wherein said first monomer series
comprises a plurality of different aromatic-aliphatic dihydroxy compounds,
each having the general structure:

wherein R_3 is selected from the group consisting of -CH=CH-, $(-CH_2-)_a$, and
-CHN(L$_1$L$_2$), in which a has a value from zero to eight, inclusive, and L$_1$ and
20   L$_2$ are independently selected from the group consisting of hydrogen and
straight and branched alkyl and alkylaryl groups containing up to 18 carbon
atoms, provided that L$_1$ and L$_2$ are not both hydrogen; R$_5$ and R$_6$ are each
independently selected from the group consisting of hydrogen and straight or
branched alkyl groups having up to 18 carbon atoms, R$_4$ is $(-CH_2-)_b$, wherein b
25   independently has a value between zero and eight, inclusive; and R$_2$ is selected
from the group consisting of straight and branched alkyl and alkylaryl groups
containing up to 18 carbon atoms.

54.   The method of claim 51, wherein said monomer series with
30   polymerizable carboxylic acid groups comprises a plurality of different
dicarboxylic acid compounds, each having the general structure:

$$HO - \overset{\overset{\displaystyle O}{\displaystyle \|}}{C} - R - \overset{\overset{\displaystyle O}{\displaystyle \|}}{C} - OH \cdot$$

wherein R is selected from the group consisting of saturated and unsaturated,

5 substituted and unsubstituted alkyl, aryl and alkylaryl groups containing up to

18 carbon atoms.

55.   The method of claim 52, wherein for one or more of said

monomers of said first monomer series, at least one of R_2, L_1 or L_2 contain at

10 least one ether linkage.

56.   The method of claim 53, wherein for one or more of said

monomers of said first monomer series, at least one of R_2, R_5, R_6, L_1 or L_2

contain at least one ether linkage.

15

57.   The method of claim 54, wherein for one or more of said

monomers of said dicarboxylic acid monomer series, R contains at least one

ether linkage.

20   58.   The method of claim 41, wherein said copolymers are further

modified by chemical reactions or cross-linking.

59   The method of claim 41, wherein said end-use properties are

measured by ELISA, SAM, chromatographic methods, DSC, TGA, DMA,

25 TMA, microscopic techniques or processing methods.

60.   The method of claim 41, wherein the end-use property that is

measured is a mechanical property, a viscoelastic property, a morphological

property, an electrical property, an optical property, solute or gas permeability,

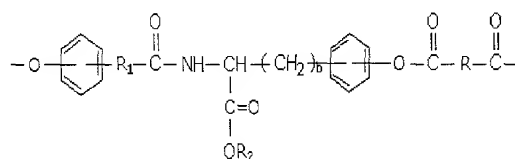30 surface tension or a thermal property.

61.   The method of claim 41, wherein the end-use property that is measured is antibacterial activity, blood compatibility, tissue compatibility, drug release characteristics, biological interactions with living organisms, hydrolytic degradation or protein adsorption characteristics.

62.   The method of claim 41, wherein the end-use property that is measured is polymer processability, radiation stability, sterilizability, adhesive properties, hydrophobic characteristics or stability to specific reaction conditions.

63.   A polyarylate comprising repeating units having the structure:

wherein R is selected from the group consisting of saturated and unsaturated, substituted and unsubstituted alkyl, aryl and alkylaryl groups containing up to 18 carbon atoms;

R_1 is selected from the group consisting of -CH=CH-, $(-CH_2-)_a$, and -CHN(L_1L_2), in which a has a value from zero to eight, inclusive, and L_1 and L_2 are independently selected from the group consisting of hydrogen and straight and branched alkyl and alkylaryl groups containing up to 18 carbon atoms, provided that L_1 and L_2 are not both hydrogen;

b independently has a value between zero and eight, inclusive; and

R_2 is selected from the group consisting of straight and branched alkyl and alkylaryl groups containing up to 18 carbon atoms; and

wherein at least one of R, R_2, and, when R_1 is -CHNL$_1$L$_2$, L_1 or L_2 contains at least one ether linkage.

64.   The polyarylate of claim 63, wherein R_1 is $-CH_2-CH_2-$, b is one and at least one of R or R_2 contains at least one ether linkage.
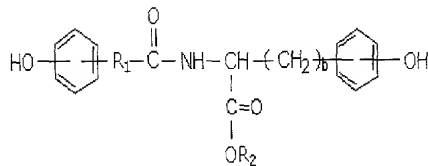
65.   The polyarylate of claim 64, wherein R_2 is selected from the group consisting of hydrogen, ethyl, butyl, octyl and benzyl, and R contains at least one ether linkage.

66.   The polyarylate of claim 65 wherein R is $-CH_2-O-CH_2-$ or $-CH_2-O-CH_2$ $-CH_2-O-CH_2-$.

67.   The polyarylate of claim 64, wherein R is selected from the group consisting of $-CH_2-C(=O)-$, $-CH_2-CH_2-C(=O)-$, $-CH=CH-$ and $(-CH_2-)_z$, wherein z is an integer between two and eight, inclusive.

68.   The polyarylate of claim 67, wherein R_2 is
$-CH_2-CH_2-O-CH_2-CH_2-O-CH_2-CH_2-OH$.

69.   A tyrosine-derived diphenol compound having the structure:

wherein R_1 is selected from the group consisting of $-CH=CH-$, $(-CH_2-)_a$, and $-CHN(L_1L_2)$, in which a has a value from zero to eight, inclusive, and L_1 and L_2 are independently selected from the group consisting of hydrogen and straight and branched alkyl and alkylaryl groups containing up to 18 carbon atoms, provided that L_1 and L_2 are not both hydrogen;

b independently has a value between zero and eight, inclusive; and

R_2 is selected from the group consisting of straight and branched alkyl and alkylaryl groups containing up to 18 carbon atoms; and

wherein at least one of R_2 or, when R_1 is -CHNL$_1$L$_2$, L$_1$ or L$_2$ contains at least one ether linkage.
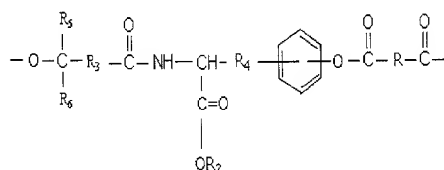
70. The diphenol of claim 69, wherein R_1 is -CH$_2$-CH$_2$-, b is one and R contains at least one ether linkage.

71. The diphenol of claim 70, wherein R_2 is
-CH$_2$-CH$_2$-O-CH$_2$-CH$_2$-O-CH$_2$-CH$_2$-OH.

72. The diphenol of claim 69, wherein R_2 is selected from the group consisting of hydrogen, ethyl, butyl, octyl and benzyl, and R_1 is -CHNL$_1$L$_2$, wherein at least one of L$_1$ or L$_2$ contains at least one ether linkage.

73. The diphenol of claim 72, wherein at least one of L$_1$ or L$_2$ is
-CH$_2$-CH$_2$-O-CH$_2$-CH$_2$-O-CH$_2$-CH$_2$-OH.

74. A poly(amide ester) comprising repeating units having the structure:

wherein R_3 is selected from the group consisting of -CH=CH-, (-CH$_2$-)$_a$, and -CHN(L$_1$L$_2$), in which a has a value from zero to two, inclusive, and L$_1$ and L$_2$ are independently selected from the group consisting of hydrogen and straight and branched alkyl and alkylaryl groups containing up to 18 carbon atoms, provided that L$_1$ and L$_2$ are not both hydrogen;

R_5 and R_6 are each independently selected from the group consisting of hydrogen and straight or branched alkyl groups having up to 18 carbon atoms;

-52-

R$_4$ is (-CH$_2$-)$_b$, wherein b independently has a value between zero and eight, inclusive;

R$_2$ is selected from the group consisting of straight and branched alkyl
5 and alkylaryl groups containing up to 18 carbon atoms; and

R is selected from the group consisting of saturated and unsaturated, substituted and unsubstituted alkyl, aryl and alkylaryl groups containing up to 18 carbon atoms; and
10

wherein at least one of R, R$_2$, R$_5$, R$_6$ and, when R$_3$ is -CHNL$_1$L$_2$, L$_1$ or L$_2$, contains at least one ether linkage.

75.   The poly(amide ester) of claim 74, wherein R$_3$ is (-CH$_2$-)$_a$ and a is
15 zero, b is one, one of R$_5$ or R$_6$ is hydrogen, the other of R$_5$ or R$_6$ is a methyl group, and at least one of R or R$_2$ contains at least one ether linkage.
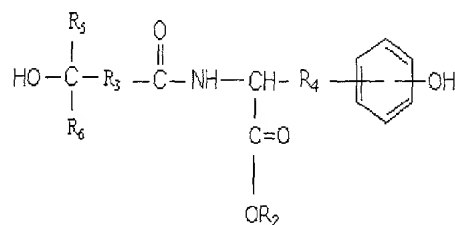
76.   The poly(amide ester) of claim 75, wherein R$_2$ is selected from the group consisting of hydrogen, ethyl, butyl, octyl and benzyl, and R contains at
20 least one ether linkage.

77.   The poly(amide ester) of claim 76, wherein R is
-CH$_2$-O-CH$_2$- or -CH$_2$-O-CH$_2$-CH$_2$-O-CH$_2$-.

25   78.   The poly(amide ester) of claim 75, wherein R is selected from the group consisting of -CH$_2$-C(=O)-, -CH$_2$-CH$_2$-C(=O)-, -CH=CH- and (-CH$_2$-)$_z$, wherein z is an integer between two and eight, inclusive.

79.   The poly(amide ester) of claim 78, wherein R$_2$ is
30   -CH$_2$-CH$_2$-O-CH$_2$-CH$_2$-O-CH$_2$-CH$_2$-OH.

80. An aliphatic-aromatic dihydroxy monomer having the structure:

$$\text{HO}-\overset{\overset{\displaystyle R_5}{|}}{\underset{\underset{\displaystyle R_6}{|}}{C}}-R_3-\overset{\overset{\displaystyle O}{\|}}{C}-\text{NH}-\overset{\underset{\underset{\underset{\displaystyle OR_2}{|}}{\underset{\displaystyle C=O}{|}}}{|}}{\text{CH}}-R_4-\underset{}{\text{\Large\bigcirc}}-\text{OH}$$

5

wherein R_3 is selected from the group consisting of -CH=CH-, $(-CH_2-)_a$, and -CHN(L_1L_2), in which a has a value from zero to two, inclusive, and L_1 and L_2 are independently selected from the group consisting of hydrogen and straight

10 and branched alkyl and alkylaryl groups containing up to 18 carbon atoms, provided that L_1 and L_2 are not both hydrogen;

R_5 and R_6 are each independently selected from the group consisting of hydrogen and straight or branched alkyl groups having up to 18 carbon atoms;

15

R_4 is $(-CH_2-)_b$, wherein b independently has a value between zero and eight, inclusive; and

R_2 is selected from the group consisting of straight and branched alkyl

20 and alkylaryl groups containing up to 18 carbon atoms; and

wherein at least one of R_2, R_5, R_6 and, when R_3 is -CHNL_1L_2, L_1 or L_2, contains at least one ether linkage.

25 81. The dihydroxy compound of claim 80, wherein R_3 is $(-CH_2-)_a$ and a is zero, b is one, one of R_5 or R_6 is hydrogen, the other of R_5 or R_6 is a methyl group, and R_2 contains at least one ether linkage.

82. The dihydroxy compound of claim 81, wherein R_2 is

30 $-CH_2-CH_2-O-CH_2-CH_2-O-CH_2-CH_2-OH$.

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83.   The dihydroxy compound of claim 80, wherein R_2 is selected from the group consisting of hydrogen, ethyl, butyl, octyl and benzyl, and at least one of R_3,R_5 or R_6 contains at least one ether linkage.

5   84.   The dihydroxy compound of claim 83, wherein one of R_5 or R_6 is hydrogen, the other of R_5 or R_6 is a methyl group, and R_3 is -$CHNL_1L_2$, wherein at least one of L_1 or L_2 contains at least one ether linkage.

85.   The dihydroxy compound of claim 83, wherein R_3 is (-CH_2-)$_a$ and 10   a is zero, and at least one of R_5 or R_6 contains at least one ether linkage.

ABSTRACT

A multi-dimensional copolymer array of a plurality of copolymers, polymerized from at least two independently variable sets of monomers, wherein the polymerization is characterized by:

5   (a)   selecting a first homologously varying series of monomers with non-varying polymerizable functional groups;

          (b)   selecting at least one additional homologously varying series of different monomers having non-varying polymerizable functional groups that are reactive with the polymerizable functional groups of the first

10   series of monomers to form copolymers; and

          (c)   separately reacting a plurality of monomers from the first monomer series with a plurality of monomers from each of the additional monomer series to form the plurality of copolymers;

          wherein the homologous variations of the monomer series are

15   selected to determine the effect of independently varying at least two different structural features of the copolymer on at least one end-use property of the copolymer.
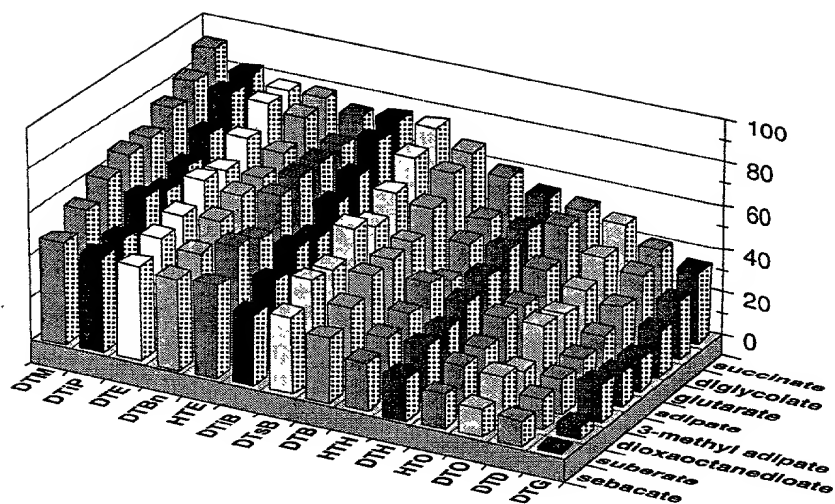
Methods for determining the effect of independently varying at least two different structural features of a copolymer and at least one end-use

20   property of the copolymer are also disclosed, in which at least one end-use property of each copolymer of the plurality of copolymers is measured and the variations in each end-use property measured for each of the copolymers is compared as a function of the homologous variation within the monomer series from which the copolymers were polymerized to determine any relationship

25   between the homologous variations and the end-use property variations among the copolymers. The method is useful for identifying members of a plurality of copolymers having useful properties for specific end-uses.
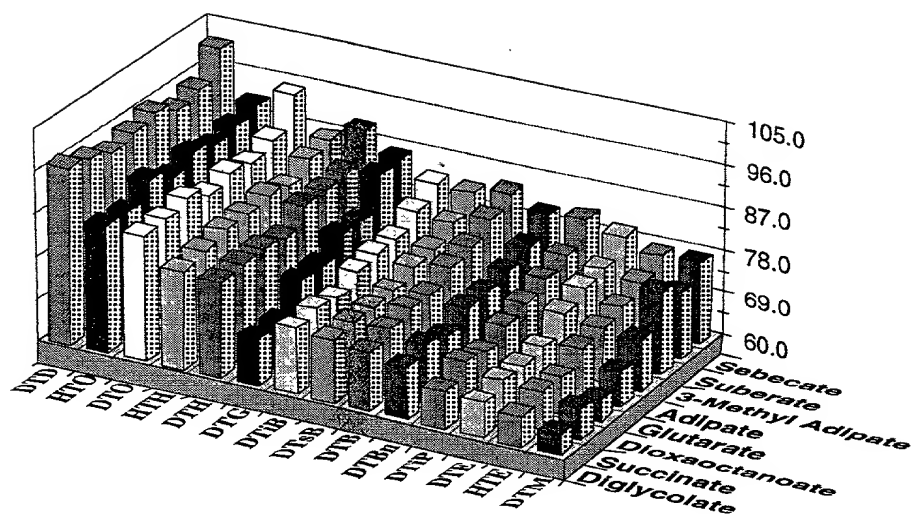
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FIG. 1

FIG. 2

FIG. 3

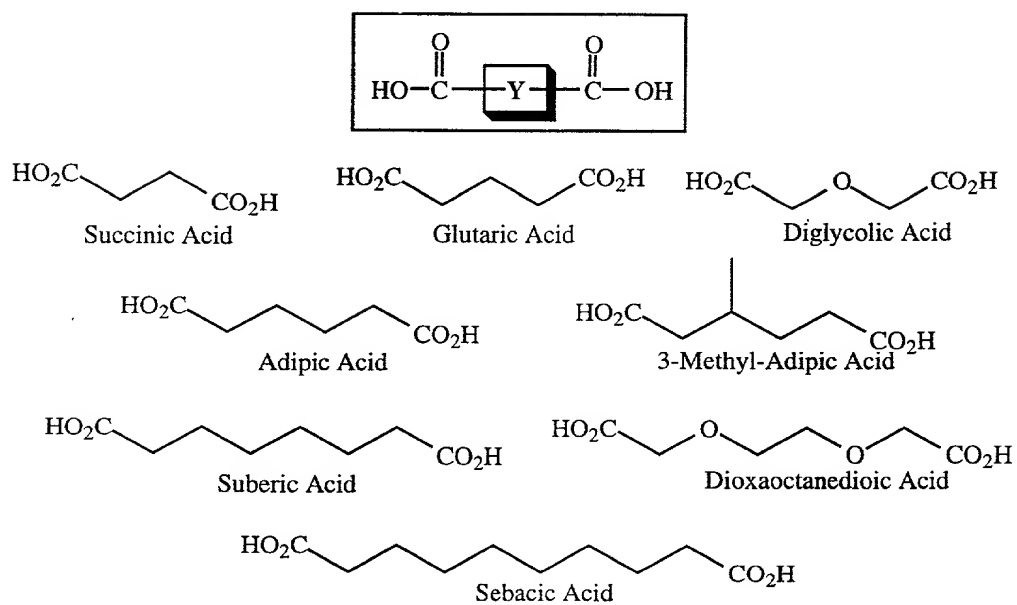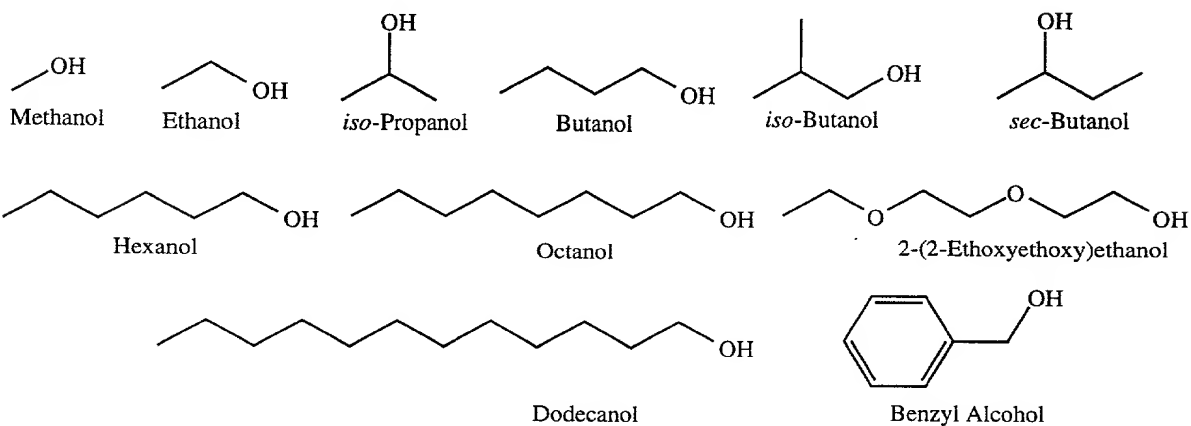# FIG. 4a

Succinic Acid

Glutaric Acid

Diglycolic Acid

Adipic Acid

3-Methyl-Adipic Acid

Suberic Acid

Dioxaoctanedioic Acid

Sebacic Acid

FIG. 4b

HO—⟨benzene ring⟩—(CH₂)ₙ—C(=O)—NH—CH—CH₂—⟨benzene ring⟩—OH

n=1,2

C=O

OR₂

Methanol   Ethanol   *iso*-Propanol   Butanol   *iso*-Butanol   *sec*-Butanol

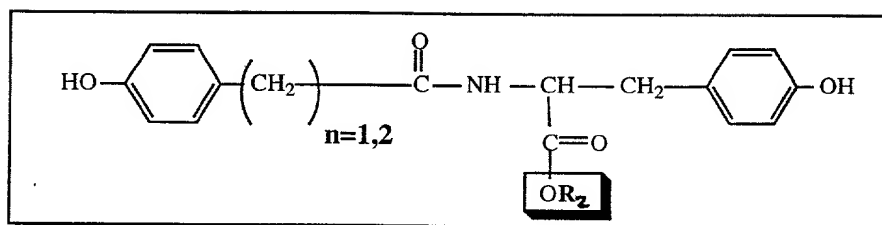Hexanol   Octanol   2-(2-Ethoxyethoxy)ethanol

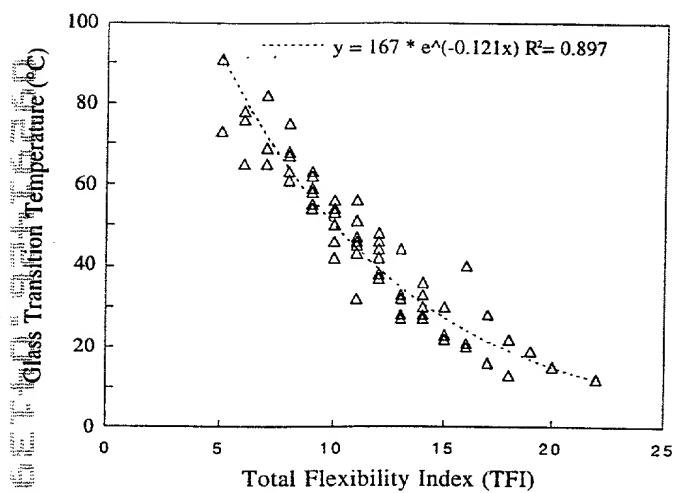Dodecanol   Benzyl Alcohol
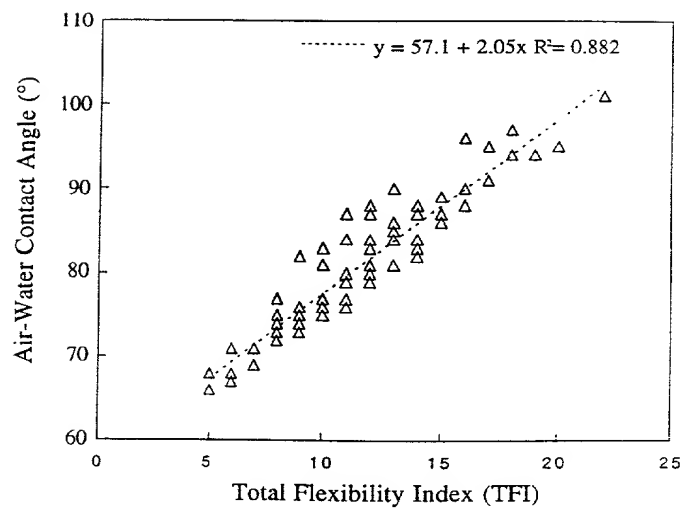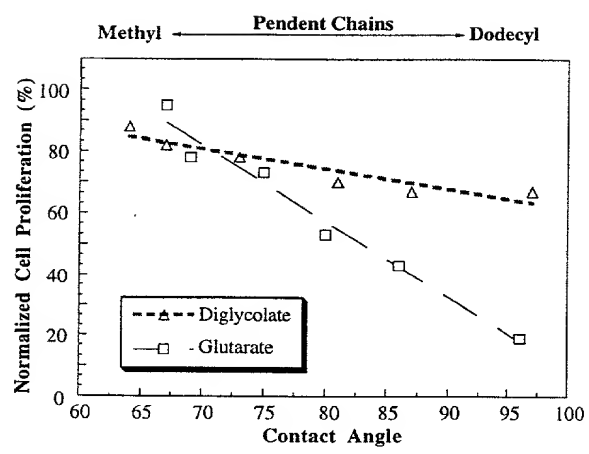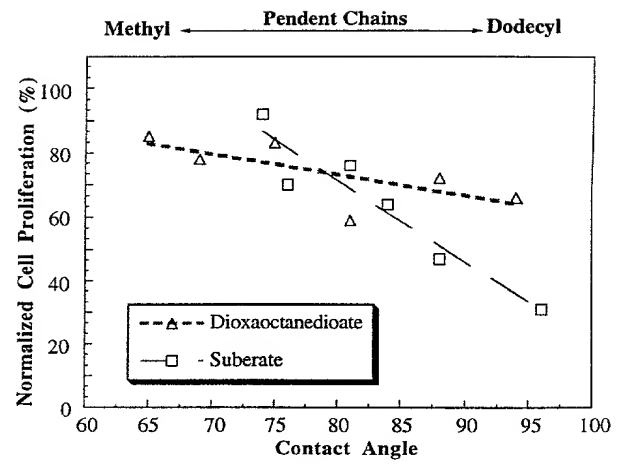
FIG. 5a

FIG. 5b

FIG. 6a

FIG. 6b

FIG. 7a

FIG. 7b

COMBINED DECLARATION AND POWER OF ATTORNEY

_____

As a below-named inventor, I hereby declare that:

My residence, post office address, and citizenship are as stated below next to my name; and

I verily believe that I am the original, first and sole inventor (if only one name is listed below) or an original, first, and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled: Construction of Copolymer Libraries, the specification of which is attached hereto.

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any Amendment referred to above.

I acknowledge the duty to disclose information which is material to the patentability of this application in accordance with 37 C.F.R. §1.56(a).

I hereby claim foreign priority benefits under 35 U.S.C. §119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of any application on which priority is claimed:

<div align="center">None</div>

I hereby claim the benefit under 35 U.S.C. §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of 35 U.S.C. §112, I acknowledge the duty to disclose material information as defined in 37 C.F.R. §1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

Application Serial No.	Filing Date	Status (patented, pending)
60/081,502	April 13, 1998	pending

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I hereby declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. §1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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